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**Enantioselective Synthesis of 2,2,5-Tri- and 2,2,5,5-Tetrasubstituted
Tetrahydrofurans and Synthesis of Diketopiperazine Containing
Natural Products**

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Natural Products**

by

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Dedication

To my family and friends, for their support and understanding during graduate school.

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Enantioselective Synthesis of 2,2,5-Tri- and 2,2,5,5-Tetrasubstituted Tetrahydrofurans and Synthesis of Diketopiperazine Containing Natural Products

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The University of Texas at Austin, 2012

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A chiral vinyl sulfoxide has been developed that undergoes highly diastereoselective Diels–Alder cycloadditions with various substituted furans in excellent yield. The cycloadducts can be stereoselectively transformed into tetrasubstituted tetrahydrofurans *via* ring-opening metathesis/cross-metathesis or oxidative cleavage and refunctionalization.

A partial synthesis of the bioactive diketopiperazine containing natural product gliocladin C was achieved in nine steps, and 13.4% overall yield. The synthesis featured several novel transformations including the construction of the core structure by an elimination and nucleophilic addition sequence, followed by a Lewis acid promoted coupling with indole giving the key quaternary oxindole intermediate. A new protocol for intramolecular reductive coupling of the oxindole and bis-unsaturated diketopiperazine led to successful construction of the hexacyclic skeleton.

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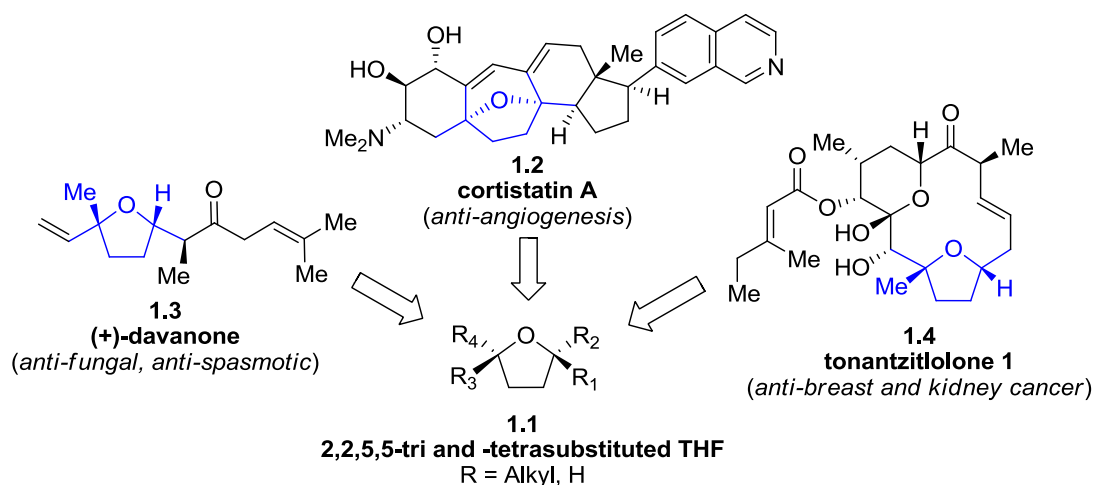
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Chapter 1: Enantioselective Synthesis of 2,2,5-Tri- and 2,2,5,5-Tetrasubstituted Tetrahydrofurans

1.1. 2,2,5-TRI AND 2,2,5,5-TETRASUBSTITUTED TETRAHYDROFURAN CONTAINING NATURAL PRODUCTS

Highly substituted tetrahydrofurans are a common structural motif found in a broad array of natural products and other biologically important molecules.^{1,2,3} Considerable attention has been given to this class of molecules due to their diverse range of biological activities that include antitumor, antimalarial, antimicrobial, and anti-angiogenesis.^{4,7} Because of the importance of these types of molecules, there has been a great deal of effort put toward the development of new methodologies to access these substructures.^{5,6} The Martin group gained an explicit interest in a class of tetrahydrofuran that is highly-substituted *only* at the 2- and 5- positions such as **1.1** (Figure 1.1). Our attention to this specific motif was spurred by our ongoing total synthesis of tetrahydrofuran-containing natural product cortistatin A **1.2**.^{7,8}

Figure 1.1: Natural products containing the 2,5-polysubstituted tetrahydrofuran moiety



While examining routes to cortistatin A (**1.2**), a survey of the literature revealed that while there were examples of the synthesis of structures similar to **1.1**, but there was not a generally applicable method for the enantioselective synthesis of these subunits.⁹ Additionally, we found that there were numerous other biologically active natural products that contained similar 2,2,5-tri or 2,2,5,5-tetrasubstituted tetrahydrofurans, such as davanone (**1.3**)¹⁰ and tonantzitlolone 1 (**1.4**).¹¹ *Thus, owing to the lack of general entries into these important substructures, we sought to develop a method that could access motifs such as 1.1 in an enantioselective manner that might find application within the synthesis of complex natural products.*

1.1. EXISTING ROUTES TO ACCESS HIGHLY SUBSTITUTED TETRAHYDROFURANS

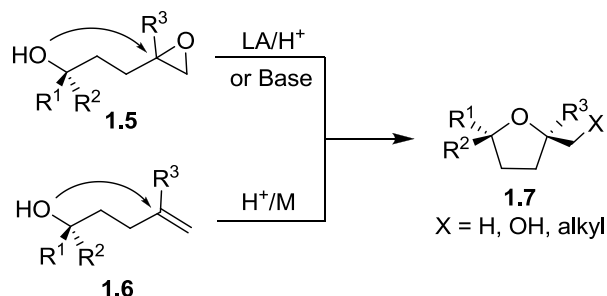
1.1.1. Acid, base, or metal promoted cyclization of ene-ols

The majority of effective methods to access 2,5-substituted tetrahydrofurans can be summarized by a few general techniques. Each section outlines a recent example of some of the most common and effective approaches within each category. Each route has advantages and disadvantages; however, none of the existing technologies were suitable for the general asymmetric synthesis of 2,2,5-tri and 2,2,5,5-tetrasubstituted tetrahydrofurans that we had in mind.

The first of such methodologies, and by far the most common approach to these pervasive heterocycles, involves the acid, base, or metal catalyzed cyclization of a 1,5-epoxy alcohol structure **1.5** or 1,5-eneol **1.6** to give tetrahydrofuran **1.7** (Scheme 1.1).⁹

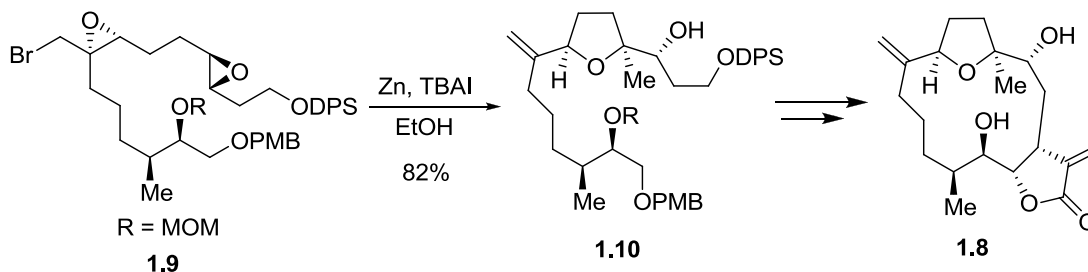
This has been widely applied to the construction of poly-tetrahydrofuran containing natural products by a ring-closure cascade.¹⁵

Scheme 1.1: Acid, base, or metal promoted cyclization of 1,5-eneols



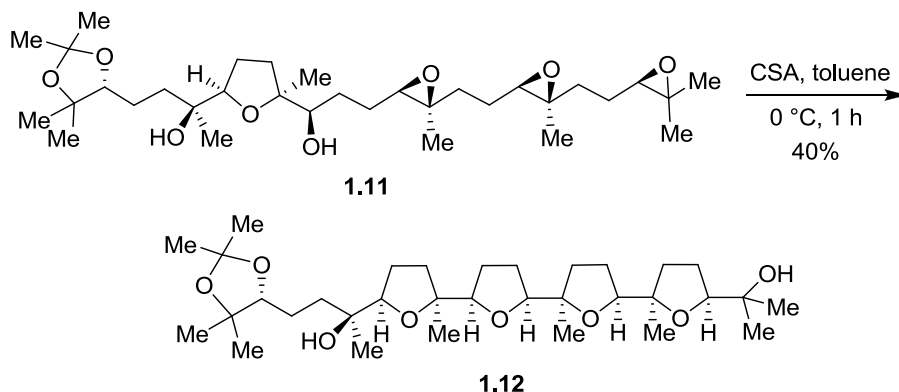
A recent example of an anionic ring closure was reported by Myers in his synthesis of the cytotoxic cembranolide uprolide D **1.8** (Scheme 1.2).¹² The bis-epoxide **1.9**, was synthesized, which has an adjacent bromide that serves as a functional handle to open the epoxide after oxidative insertion by zinc metal. Nucleophilic attack of the resultant anion opened the proximal epoxide giving 2,2,5-trisubstituted tetrahydrofuran **1.10** in 82% yield. Further transformations led to the final target **1.8**. In general, this method works well for tetrahydrofurans with minimal substitution at the 2- and 5- positions; however, the yield and diastereoselectivity decreased when trying to form 2,2,5,5-tetrasubstituted tetrahydrofurans.^{13,14} Additionally, as steric bulk around the epoxide increases, competing tetrahydropyran formation becomes a problem.^{9,15}

Scheme 1.2: Myer's anionic ring-closure to form tetrahydrofurans



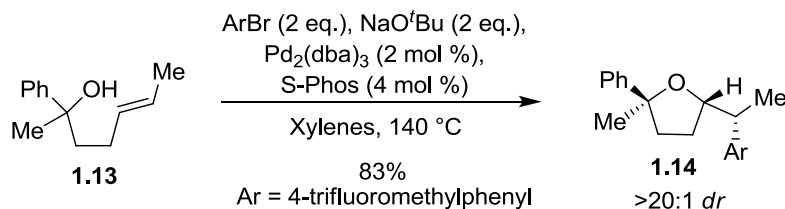
An example of a protic-acid catalyzed synthesis of poly-tetrahydrofurans was performed by Morimoto in his total synthesis of (+)-omaezakianol (Scheme 1.3).¹⁶ In the key transformation, camphorsulfonic acid was used to initiate a sequential 5-*exo*-tet cascade oxacyclization of triepoxy alcohol **1.11**, giving key intermediate **1.12** in 40% yield. This type of cascade ring closure is the most commonly used method for the construction of poly-tetrahydrofuran targets. This type of cyclization is characterized by lower yields and poor diastereoselectivity when forming tetra-substituted tetrahydrofurans.¹⁷ It also requires the multi-step synthesis of complex starting materials containing multiple pre-set stereocenters. Additionally, as with the previous example, competing tetrahydropyran formation can be a problem with increased steric bulk of the substituents around the epoxide.¹⁸

Scheme 1.3: Morimoto's sequential oxacyclization in the synthesis of (+)-omaezakianol



A lesser used technique for the preparation of highly substituted tetrahydrofurans involves the metal catalyzed carboetherification of acyclic internal alkenes. Wolfe and coworkers reported the stereoselective synthesis of tetrahydrofurans containing up to three stereocenters (Scheme 1.4).¹⁹ The authors used a palladium catalyst to cyclize tertiary alcohols such as **1.13** onto disubstituted olefins; subsequently coupling to aryl bromides, gave trisubstituted tetrahydrofurans such as **1.14** in good yield and diastereoselectivity. A Disadvantage to this method is the requirement of having an aromatic group appended to the resultant tetrahydrofuran ring. Furthermore, diastereoselectivity decreases with increased steric bulk of the substituents around the alcohol or olefin or when cyclizing to form tetrasubstituted tetrahydrofurans.^{20,21}

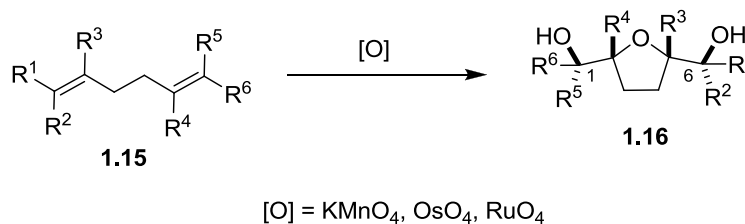
Scheme 1.4: Palladium catalyzed carbocyclization to give tetrahydrofurans



1.1.2. Oxidative cyclization of 1,5-dienes

The oxidative cyclization of 1,5-dienes has recently emerged as one of the most capable methods to access THFs in a single step (Scheme 1.5).²² cyclization of the diene **1.15** using metal oxidants such as potassium permanganate, osmium tetroxide, or ruthenium tetroxide gives highly oxidized tetrahydrofurans such as **1.16**. This methodology features the creation of four chiral carbons from a simple diene, as well as the introduction of two new alcohols at the C1 and C6 carbons of **1.16**. It suffers the similar disadvantages to the ene-ol cyclization, in that yield²³ and selectivity²⁴ drop drastically when forming tetrasubstituted tetrahydrofurans. The oxidation requires the use of harsh reagents, and yields are often poor. Furthermore, there are few options to do this type of reaction enantioselectively.²⁵

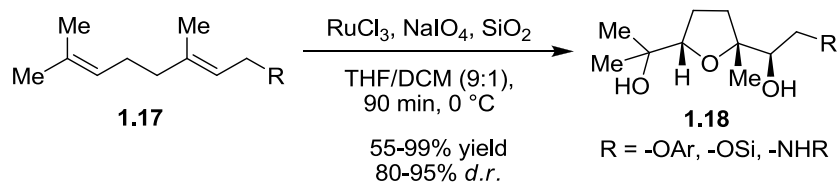
Scheme 1.5: Oxidative cyclization of 1,5-dienes



In a procedure developed by Stark and co-workers, 1,5-dienes **1.17** induced to undergo oxidative cyclization with ruthenium tetroxide and sodium periodate as the terminal oxidant (Scheme 1.6).²⁶ This oxidation improves upon previous oxidative cyclization techniques and gives tetrahydrofurans **1.18** in good to excellent yields and diastereoselectivities while maintaining a very low catalyst loading. This method was

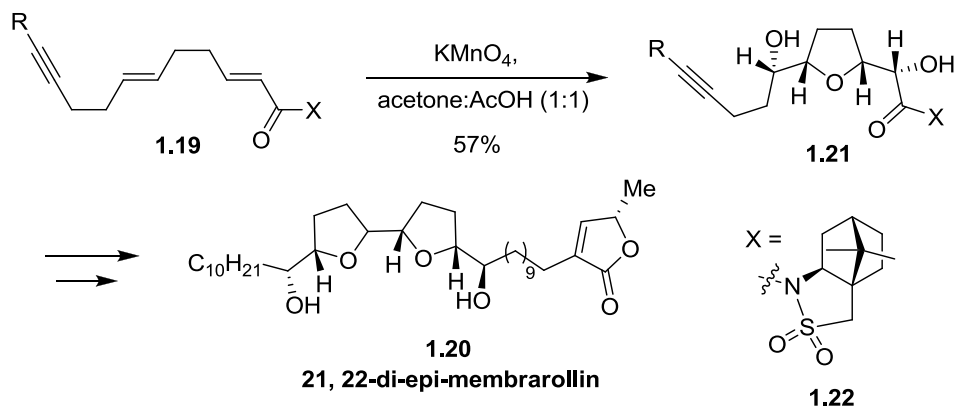
established for a wide variety of substrates and proved to be applicable for the formation of trisubstituted tetrahydrofurans, but not 2,2,5,5-tetrasubstituted tetrahydrofurans.

Scheme 1.6: Ruthenium tetroxide catalyzed oxidative cyclizations



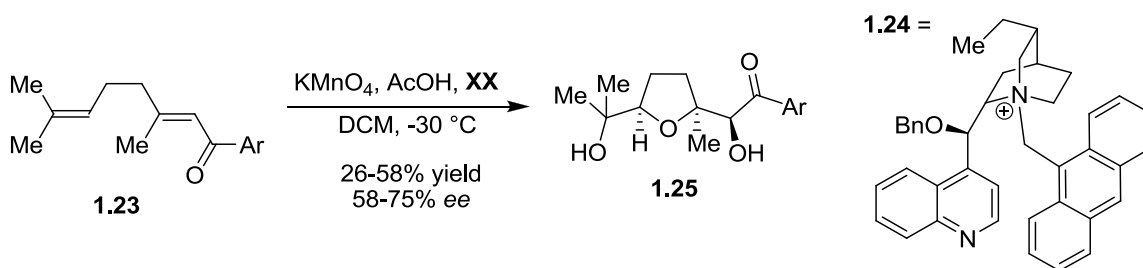
Brown and co-workers published an unusual example of a diastereoselective oxidative cyclization of yne-diene **1.19** in their total synthesis of 21,22-di-epimembrarollin (**1.20**).²⁷ A metal-oxo-mediated oxidative cyclization gave di-substituted tetrahydrofuran **1.21** as a single isomer in 57% yield (Scheme 1.7). The selectivity was directed by camphorsultam auxiliary **1.22**. Tetrahydrofuran **1.21** was then carried through a second oxo-cyclization and then onto the final target **1.20**. Similar examples of stereoselective oxidative cyclization with 2,2,5,5-tetrasubstituted tetrahydrofurans are rare, presumably due to poorer selectivity and yields.

Scheme 1.7: Stereoselective synthesis of 21,22-di-epi-membrarollin



Brown and Keily obtained moderate levels of enantioselection by performing the oxidation of 1,5-dieneones **1.23** in the presence of substoichiometric amounts of chiral tertiary ammonium salt **1.24** (Scheme 1.8).²⁸ The cyclization, which was performed under biphasic conditions, gave trisubstituted tetrahydrofurans **1.25** in low to moderate yield, and isolated as a single diastereomer. This reaction is not preparatively useful at this time due to the low yields and enantioselectivity, future iterations of this type of methodology may be valuable synthetic tools.

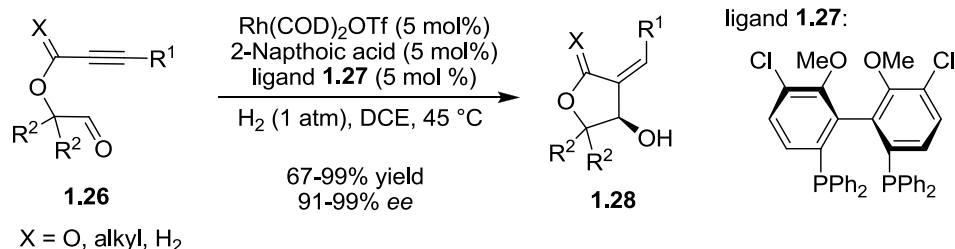
Scheme 1.8: Enantioselective oxidative cyclization by phase transfer catalysis



1.1.3. Reductive cyclization of acetylenic aldehydes

Recent reports by Krische and co-workers showcased the utility of a rhodium-catalyzed reductive cyclization of acetylenic aldehydes (Scheme 1.9).²⁹ They cyclized a variety of aldehydes such as **1.26** in the presence of 5% rhodium catalyst and the chiral ligand **1.27** to give densely functionalized tetrahydrofuran cores such as **1.28**. Yields for this process were generally good, ranging from 67 to 99%. Enantioselectivity of the reaction is excellent at 91-99% enantiomeric excess. This method worked extremely well to access densely functionalized tetrahydrofurans such as **1.28**; however, the route is not applicable 2,2,5-tri and 2,2,5,5-tetra-substituted tetrahydrofuran cores (**1.1**) that have no substitution at the 3- and 4-positions.

Scheme 1.9: Highly enantioselective reductive cyclization of acetylenic aldehydes

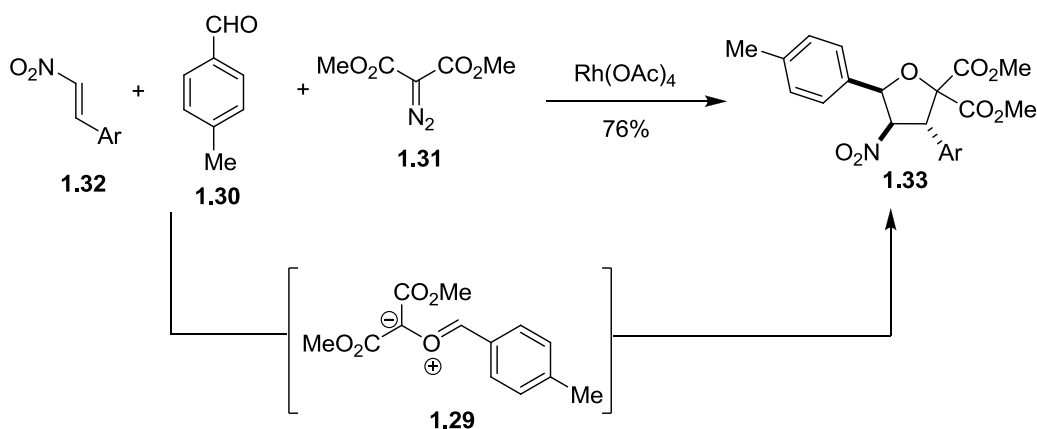


1.1.4. Synthesis of substituted tetrahydrofurans *via* cycloaddition

A powerful strategy for preparation of substituted tetrahydrofuran substructures uses a [3+2] cycloaddition to generate a five-membered ring. One common and effective approach to this construction involves the rhodium-catalyzed reaction of a stabilized diazo-compound and aldehyde, followed by cycloaddition with an activated olefin. One

recent example of this type of transformation is the rhodium tetraacetate catalyzed generation of carbonyl ylide **1.29** from aryl aldehyde **1.30** and dimethyl diazomalonate (**1.31**) (Scheme 1.10).³⁰ Intermediate **1.29** underwent a [3+2] cycloaddition with activated olefin **1.32**, giving substituted tetrahydrofuran **1.33**, as a single diastereomer. Transformations such as this are severely limited by the types of functionality and substitution that can be present on each reactive unit. For example, the olefin must be activated by a strongly electron withdrawing group, and the diazo-component must be stabilized by adjacent ketones. Furthermore the ylide must be derived from an aryl substituted aldehyde or ketone in order to achieve good yields and selectivities.

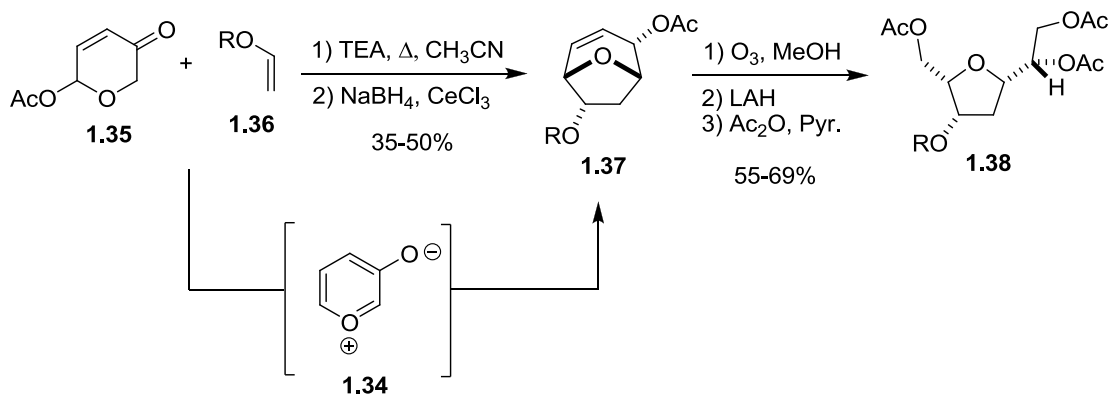
Scheme 1.10: [3+2] cycloaddition of aryl aldehydes to give substituted tetrahydrofurans



Fishwick and co-workers have reported a sequence involving a [3+2] cycloaddition followed by oxidative ring-opening to access highly-functionalized, substituted tetrahydrofurans.³¹ The route consists of generating of a highly reactive 3-oxidopyriliium betaine **1.34** by heating pyranone **1.35** in the presence of base. Betaine

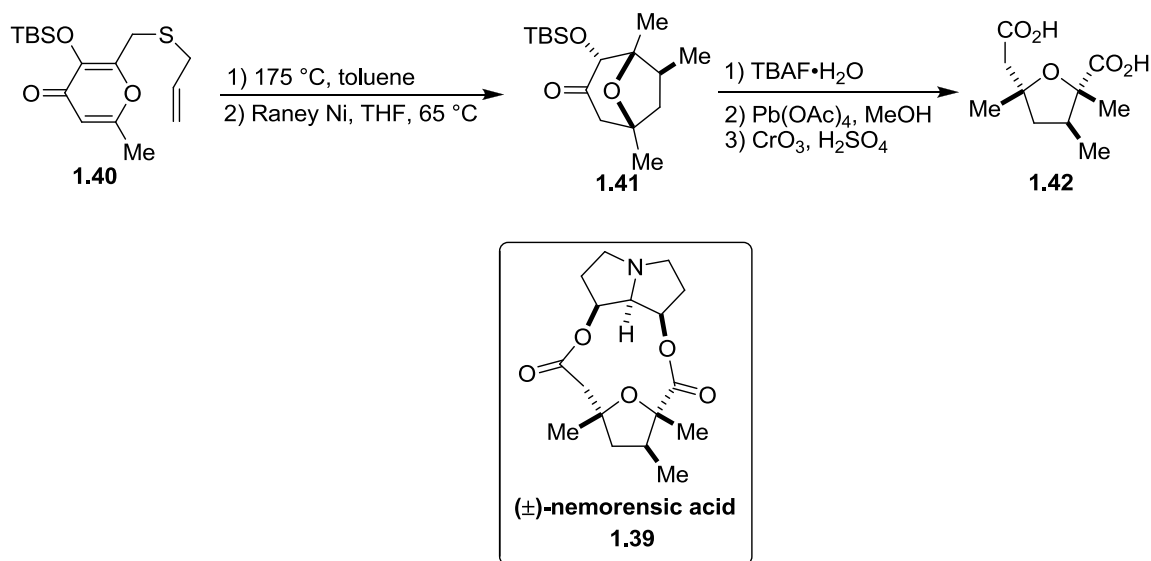
1.34 then cyclized with electron rich olefin partners such as **1.36** to give cycloadducts **1.37** after a diastereoselective reduction (Scheme 1.11). Cycloadduct **1.37** was cleaved by exposure to ozone. Reduction of the resultant aldehydes with lithium aluminum hydride, and acylation of the resultant alcohols led to tetrahydrofuran **1.38** as a single diastereomer in moderate yields. Despite the good selectivity, the poor yields and the fact that this route, to the best of our knowledge, has not been applied to prepare more complex tetra-substituted tetrahydrofurans limits its usefulness.

Scheme 1.11: Oxidative cleavage of 3-oxidopyrilium betaine-derived cycloadducts



Mascarenas and co-workers reported a route to the core of racemic (\pm)-nemorensic acid **1.39** by an intramolecular [5+2] cycloaddition of **1.40** (Scheme 1.12).³² The resulting oxabicyclo[3.2.1]octane **1.41** was elaborated to the core structure **1.42** by silicon deprotection, oxidative cleavage with lead tetraacetate, and Jones oxidation.³³ This route constitutes a method to access 2,2,5,5-tetrasubstituted tetrahydrofuran cores, but it suffers from a high step count.

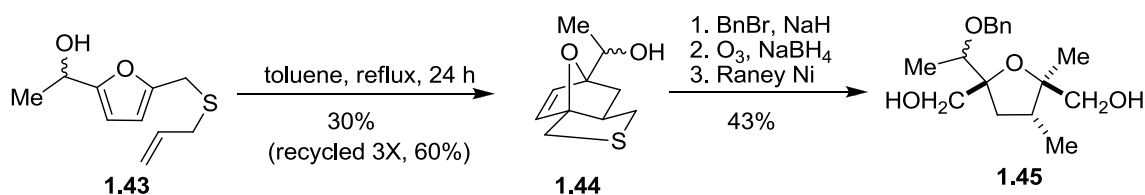
Scheme 1.12: [5+2] Pyrone-alkene cycloaddition approach to tetrahydrofurans



The [4+2] cycloadditions between substituted furans and dienophiles has been used to construct bicyclic systems.^{34,35} These structurally rigid norbornene derivatives may then undergo ring opening to give substituted tetrahydrofurans. For example, Klein and co-workers heated 2,5-disubstituted furan **1.43** to induce an intramolecular Diels-Alder reaction to give bridged oxa-bicycle **1.44** in 60% yield overall after three recycles of the starting material (Scheme 1.13).³⁶ A likely reason for the poor conversion during the Diels-Alder cycloaddition is that furan is considered a moderately reactive diene, and generally requires forcing conditions to cyclize with unactivated olefins.^{37,38,39,40} With **1.44** in hand, protection of the free alcohol, ozonolysis, and desulfurization led to 2,2,5,5-tetrasubstituted tetrahydrofuran **1.45** in low yield. This approach is notable because, despite its poor yields, this strategy of furan Diels-Alder followed by ring-cleavage

serves as a very direct way to access highly substituted tetrahydrofurans from simple starting materials, and serves as useful precedent for our approach to tetrahydrofuran synthesis.

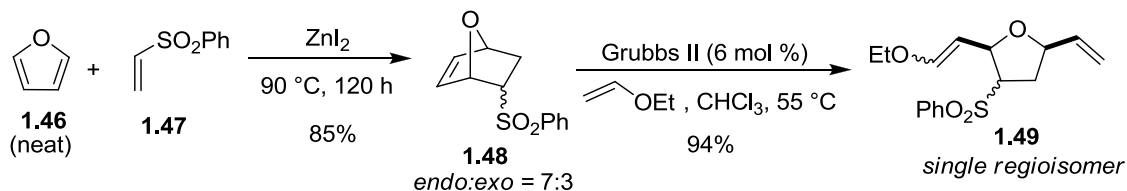
Scheme 1.13: Intramolecular Diels-Alder reaction followed by oxidative ring-opening



Similarly relevant was some recent work by Rainier and co-workers, who promoted the reaction of furan (**1.46**) with phenylvinyl sulfone (**1.47**) under Lewis-acid promoted conditions to give endo-substituted oxabicyclic **1.48** (Scheme 1.14).^{41,42} This bicycle was then opened in a highly regioselective manner using Grubbs 2nd generation catalyst in the presence of excess ethyl vinyl ether to give the disubstituted tetrahydrofuran **1.49** as a single regioisomer. While the origin of the high regioselectivity is unknown, it was suggested that it was directed by either an electronic or steric effect from the sulfone group. *This technique of ring-opening cross metathesis caught our attention as a useful tool for the rapid synthesis of a diverse array of tetrahydrofurans from a single simple starting material, and it served as additional inspiration for our developing methodology. Encouraged by this precedent, we sought to develop a methodology that would permit for the construction of 2,2,5,5-tetrahydrofurans that was enantioselective, low in step count, and generally applicable to a variety of targets. To*

accomplish this, we would need to develop a technique for the removal any substituents from the 3- and 4- positions of the tetrahydrofuran.

Scheme 1.14: Regioselective ring-opening cross metathesis strategy

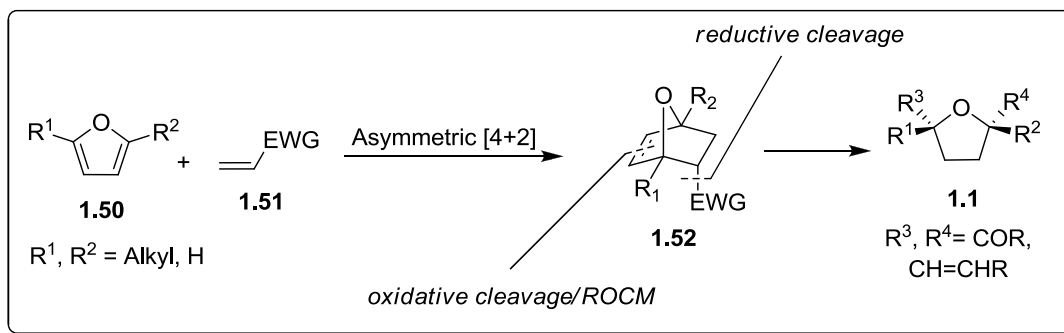


1.2. THE MARTIN GROUP APPROACH TO THE ENANTIOSELECTIVE SYNTHESIS OF 2,2,5-TRI- AND 2,2,5,5-TETRASUBSTITUTED TETRAHYDROFURANS

1.2.1. Martin group strategy to access 2,2,5-tri- and 2,2,5,5-tetrasubstituted tetrahydrofurans and key challenges

As mentioned previously, our goal was to develop a methodology to access enantioenriched, highly substituted tetrahydrofuran cores related to scaffold **1.1** (Scheme 1.X). This would not only allow us to access the core of a number of natural products, but it would also provide a means to synthesize a wide variety of tetrahydrofuran cores from simple starting materials. The enantioselective approach, along with the use of simple and inexpensive starting materials, are key requirements for our route, because we hope to apply this methodology to multistep total synthesis. Based on inspiration from our ongoing total synthesis of cortistatin A, along with the aforementioned literature examples, we conceived of the general strategy for access into 2,2,5-tri- and 2,2,5,5-tetrasubstituted tetrahydrofuran cores **1.1** as outlined in Scheme 1.15.

Scheme 1.15: Martin group strategy to access enantioenriched tetrahydrofurans



The plan begins with an intermolecular asymmetric [4+2] cycloaddition between the furan **1.50**, which is substituted at the 2- and/or 5-positions and an activated olefin represented as **1.51**. This stereoselective Diels-Alder reaction, directed by either a chiral Lewis-acid or chiral auxiliary, would lead to the enantioenriched oxanorbornene cores **1.52** (Scheme 1.1.15). The critical requirement for this cycloaddition is to achieve a preparatively useful, stereoselective Diels-Alder reaction, that is suitable for use in multistep synthesis. With this in mind, we faced a number of unique challenges. (1) Due to the fact that we will be preparing substituted furans as a starting material, use of a large excess of furan must be avoided. Lowering the stoichiometry of furan will be a challenge since Diels-Alder reactions of furan generally require a large excess of furan.^{38,39,37} (2) Owing to the poor reactivity of furan, we require the use of a dienophile that is activated with an electron withdrawing group in order to achieve good reactivity. This activating group must be removed later in the synthesis, so that we may access tetrahydrofurans that are either unsubstituted or minimally substituted at the 3- and 4- positions such as **1.1**. (3) When using a Diels-Alder reaction to construct more complex systems, selectivity involves an enantioselective component, along with regio-, and diastereoselectivity

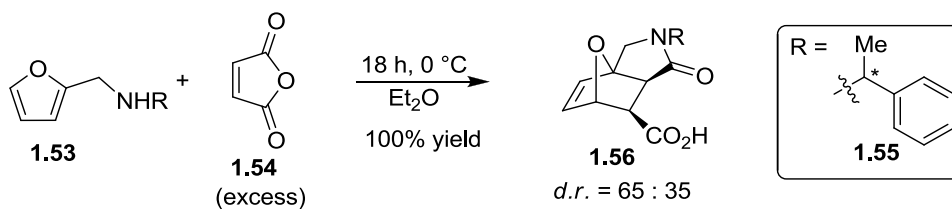
components (*endo/exo* ratio). We require a highly selective Diels-Alder reaction, so the use of high temperatures must be avoided in order to maintain stereoselectivity.

The second stage of the sequence in Scheme 1.15 involves the ring-opening of the oxabicycle **1.52**, followed by refunctionalization of the electron-withdrawing group to give the target tetrahydrofuran **1.1**. We envisioned two potential options for this step. The first option involved the oxidative cleavage of the olefin to give ketones, esters, or aldehydes as products (*e.g.*, **1.1**, $R^3, R^4 = \text{CHO}, \text{CO}_2\text{H}, \text{CO}_2\text{R}$). The second option involving a ring-opening cross metathesis (ROCM) reaction to give heterocycles such as **1.1** ($R^3, R^4 = \text{CH=CHR}, \text{CH=CH}_2$). The key challenge for this ring opening is finding suitable conditions to achieve a fully regioselective cross metathesis, so a mixture of regioisomers of **1.1** was not obtained.

1.2.2: Overview of existing methodology for the enantioselective Diels-Alder cycloaddition with furans

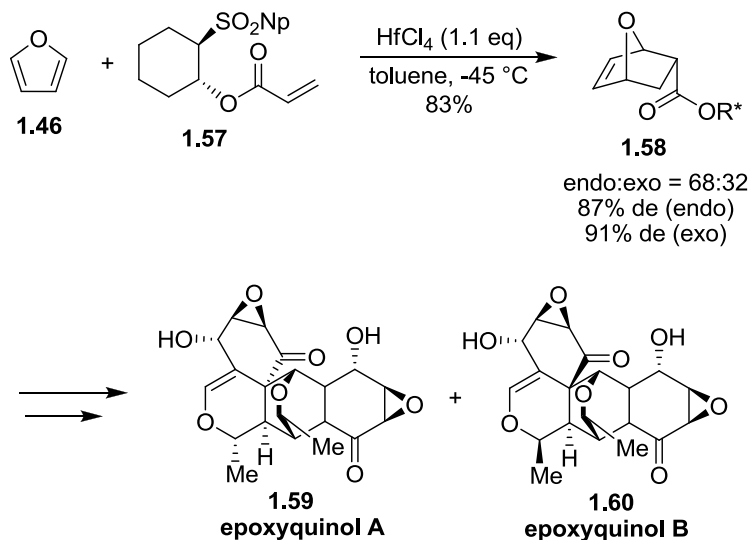
A survey of the literature reveals that there are many excellent methodologies for inducing enantioselective Diels-Alder reactions, but there are few technologies that use furan as the diene partner. One such example of the enantioselective [4+2] cycloaddition involving furan is the cycloaddition between chiral 2-methylaminofuran **1.53** and maleic anhydride (**1.54**) (Scheme 1.16).⁴³ The chiral α -methyl-benzyl substituent **1.55** induces the diastereoselectivity of the tricyclic product **1.56**. The reaction proceeded in excellent yield; however, it failed to achieve a useful (>90%) level of diastereoselection. For our methodology, ring-opening of tricycles such as **1.56** would result in a tetrahydrofuran that has substitution at the 3- and 4- positions that would be tedious for us to remove, thus is it not of practical interest to us as a possible starting point.

Scheme 1.16: Early example of an enantioselective Diels-Alder reaction with a furan



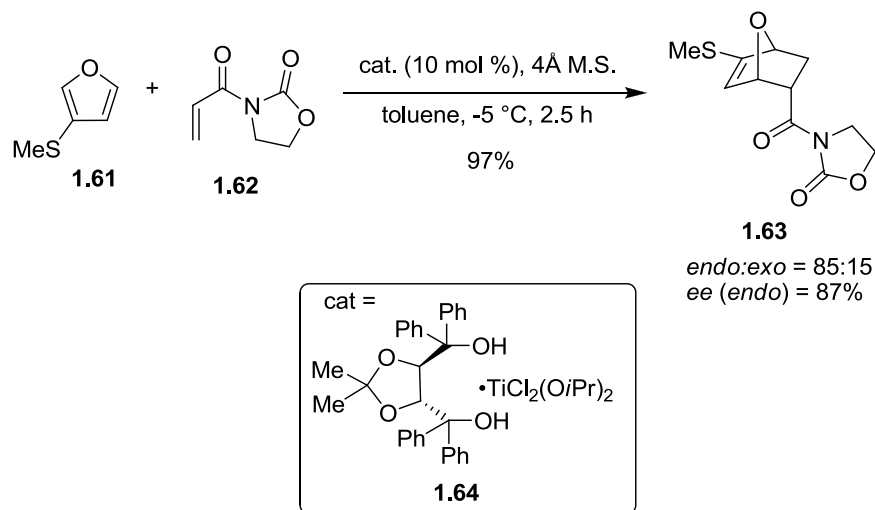
Hayashi and co-workers reported the Lewis acid-promoted Diels-Alder reaction between furan (**1.46**) and the chiral acrylate derivative **1.57** (Scheme 1.17).⁴⁴ The chiral acrylate **1.57**, which was originally developed by Corey and Sarakinos,⁴⁵ combined with Hayashi's low temperature conditions, using HfCl₄ as a stoichiometric promoter, led to good selectivities and yields. While they achieved good diastereomeric excess at 87% for the major *endo* product and 91% for the *exo* product, the *endo:exo* ratio was only 7:3. They later used this methodology in their total syntheses of epoxyquinols A (**1.59**) and B (**1.60**).⁴⁶

Scheme 1.17: Hayashi's HfCl_4 promoted Diels-Alder with furan and chiral acrylate



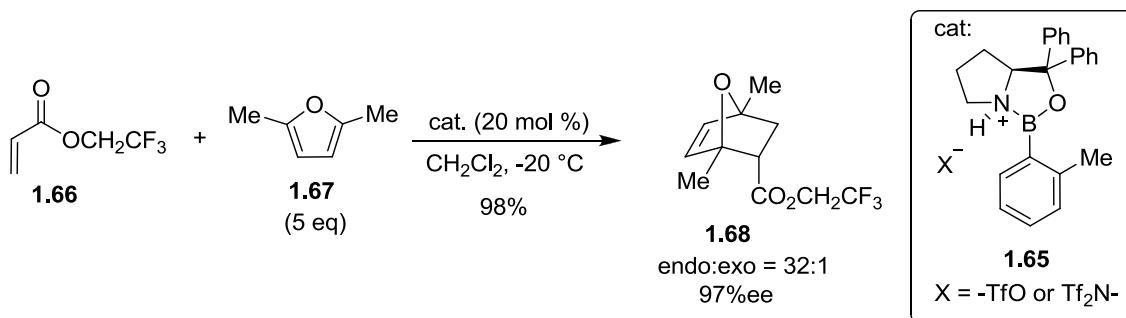
Narasaka and co-workers developed a useful catalytic system to induce the cycloaddition between the electron rich furan **1.61** and the acryloyl oxazolidinone **1.62**, to give the oxabicycloheptene derivative **1.63** (Scheme 1.18).⁴⁷ Using a 10% loading of the chiral Lewis acid **1.64**, they were able to catalyze the cycloaddition in excellent yield and good *endo:exo* selectivity and enantiomeric excess. However, this method has not been applied to other types of furans.

Scheme 1.18: Chiral Lewis acid directed enantioselective furan Diels-Alder reaction



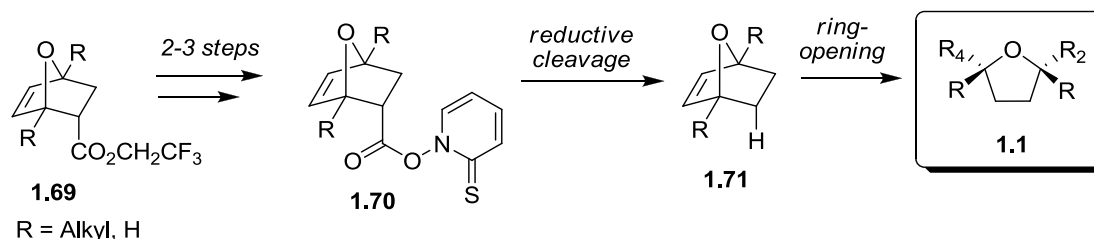
Corey and co-workers have recently developed what is arguably the most impressive technology to date for the enantioselective Diels-Alder of a furan.⁴⁸ Using a variant of his signature chiral oxazaborolidine catalyst **1.65** as a Lewis acid to promote the [4+2] cycloaddition of activated trifluoroethyl acrylate **1.66** and 2,5-dimethylfuran (**1.67**) (Scheme 1.19), the cycloadduct **1.68** was obtained in 98% yield, 97% enantiomeric excess, and 32:1 *endo:exo* selectivity. The excellent yields and selectivity prompted us to closely examine this technology for possible application to our own methodology and total synthesis goals.

Scheme 1.19: Corey's oxazaborolidine catalyzed Diels-Alder with furans



While Corey's methodology achieved impressive results, it faces a major downside when trying to access target tetrahydrofurans such as **1.1**. Namely, trifluoroethyl-ester auxiliary must be cleaved from the molecule **1.69** (Scheme 1.20). The most likely approach for removing an ester group from substituted oxanorbornene **1.69** would be by a hydrolysis of the ester followed by a trans-esterification to make Barton-ester **1.70**.⁴⁹ This activated ester can then undergo a radical decarboxylation to give **1.71**, which, after ring-opening leads to the tetrahydrofuran structure **1.1**. Because auxiliary cleavage process would add two or three steps to the sequence, we looked for an alternative activating group that could be more readily cleaved or re-functionalized than the ester group of **1.68**.

Scheme 1.20: The multi-step cleavage of an ester functional group



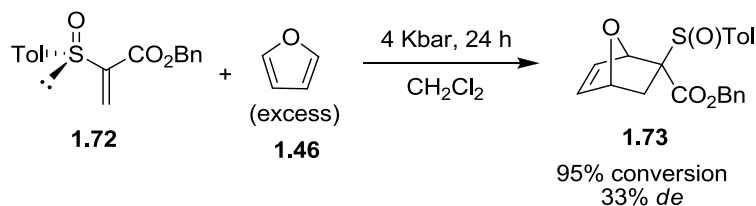
The ideal activating group for a dienophile would be one that could be removed in a single step. It would thus act as an ethylene equivalent in the Diels-Alder reaction, leading directly to oxabicycles such as **1.71** without significant manipulation. With this in mind, we turned our attention toward vinyl sulfoxides and vinyl sulfones as potential activating groups. Sulfones and sulfoxides are known to be readily cleaved under reductive conditions or converted to a ketone or alcohol in a single step.^{50,51,52}

1.2.3: Overview of existing methodology for the enantioselective Diels-Alder cycloaddition with chiral sulfones or chiral sulfoxide activating groups.

With the aim of finding a suitable sulfone or sulfoxide-activated dienophile for our methodology, we surveyed the literature possibilities. While a number of vinyl sulfones and sulfoxides have been used for asymmetric Diels-Alder reactions, only a few led to good yields and stereoselectivities, and were potentially be readily cleavable from the molecule.

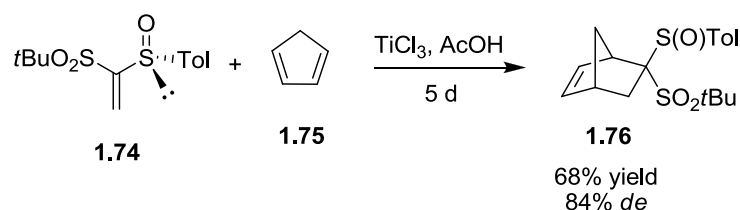
One early example was reported by Ruano and co-workers, who performed an asymmetric cycloaddition between chiral vinyl sulfoxide **1.72** and furan (**1.46**) under high pressure (Scheme 1.21).⁵³ Under these forcing conditions, they were obtained high conversion to the *endo*-product **1.73**, but the enantioselectivities were low. Even if the enantioselectivity could be improved, the additional benzyl-ester substituent hinders its ability to be used as an ethylene equivalent, and is thus not well-suited for our goal.

Scheme 1.21: Ruano's chiral sulfoxide directed dienophile



Using the related chiral vinyl sulfoxide **1.74**, Carretero and co-workers performed a cycloaddition with cyclopentadiene (**1.75**) in the presence of titanium tetrachloride as a Lewis-acid promoter to give cycloadduct **1.76** in 68% yield (Scheme 1.22).⁵⁴ The diastereoselectivity under these conditions was good, and the resulting product, **1.76**, possessed two carbon-sulfur bonds, which could theoretically be cleaved from the molecule in a single step. This would allow **1.74** to act as a masked ethylene dienophile. However, this cycloaddition was not examined using furan as the diene partner. Furan **1.46** is a significantly poorer cycloaddition partner than cyclopentadiene (**1.75**); so, this sluggish five day long reaction does not hold promise to be applicable with furans.

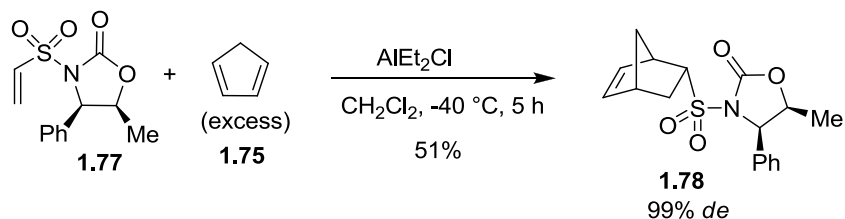
Scheme 1.22: Carretero's bis-substituted chiral dienophile



Chiral vinyl sulfonamide **1.77**, which was prepared by the Bernabeu group from norephedrine, was used to achieve a highly selective Diels-Alder cycloaddition with an excess of cyclopentadiene (**1.75**) (Scheme 1.23).⁵⁵ The reactions were performed at -40 °C in the presence of a Lewis acid, giving only the *endo*-adduct **1.78** in 99%

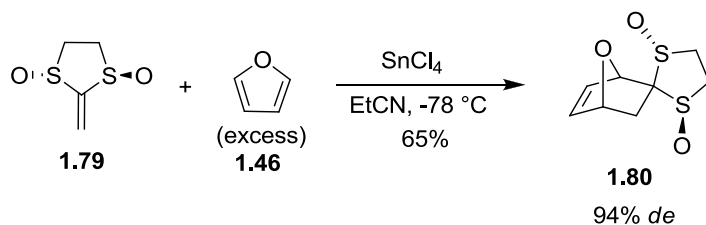
diastereoselectivity. Although the selectivity is impressive, this novel dienophile has not been demonstrated to react with furans.

Scheme 1.23: Highly selective norephedrine derived chiral vinyl sulfonamide dienophile



Aggarwal and co-workers used bis-sulfoxide **1.79** as a dienophile that reacted with furan (**1.46**) in the presence of a Lewis acid, to deliver **1.80** with 94% diastereoselectivity and in 65% yield (Scheme 1.24).⁵⁶ We became interested in this dienophile due to the high selectivity and the fact that the bis-sulfoxide moiety could possibly be cleaved from the molecule in a single step under reductive conditions.⁵⁷

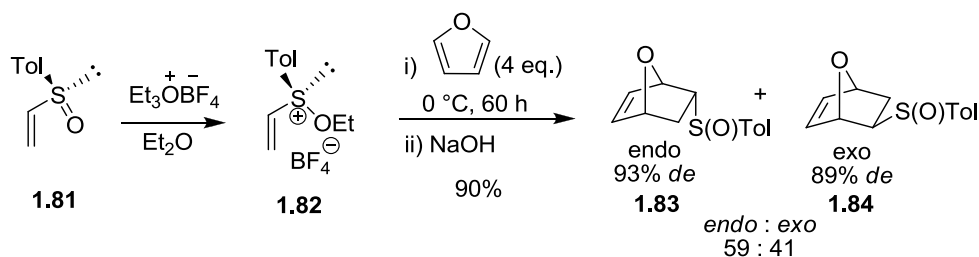
Scheme 1.24: Use of Aggarwal's bis-sulfoxide dienophile



Kagan's group has developed one of the most reactive and selective chiral vinyl sulfoxides reported to date. Kagan began with known chiral vinyl sulfoxide **1.81** and

activated it with Meerwein's salt, giving the active sulfoxonium species **1.82**, which was used directly in the next step (Scheme 1.25).^{58,59} After stirring salt **1.82** with furan at 0 °C for several days, they isolated a mixture (3:2) of *endo*-cycloadduct **1.83** and *exo*-product **1.84**. This cycloaddition is notable because it represented the first example involving furan that was both highly diastereoselective and high yielding. However, there are disadvantages to this methodology, including the requirement of an extra alkylation step to prepare the sulfoxonium intermediate **1.82** and the need for a strongly basic workup in order to cleave the O-alkyl group and generate **1.83** and **1.84**.

Scheme 1.25: Kagan's highly diastereoselective Diels-Alder reaction

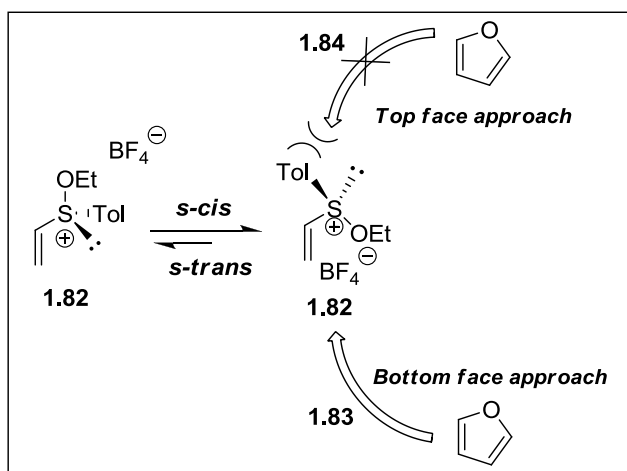


Sulfoxonium salt **1.82** (Scheme 1.25) and bis-sulfoxide **1.79** (Scheme 1.24) have exhibited the highest reported diastereomeric excesses for the reaction of any known chiral vinyl sulfoxide or sulfoxonium salt with furan. The use of these dienophiles could be optimized and expanded to be 2,5-disubstituted furans, it would constitute a useful means for the synthesis of enantioenriched oxabicycles. These oxabicycles, that could be elaborated into 2,2,5,5-tetrahydrofurans. Both of these dienophiles **1.79** and **1.82** were studied for adaption to our methodology to access tetrahydrofuran cores represented by **1.1**.

1.2.4. Proposed selectivity model for chiral vinyl sulfoxides

Diastereoselectivity in Diels-Alder reactions employing chiral vinyl sulfoxides is believed to be a consequence of two factors: the approach of the diene to the least sterically crowded face of the vinyl sulfoxide and the restriction of the dienophile to a single reactive *s-cis* conformation.^{60,61} Sulfoxonium salt **1.82**, as suggested by Ronan and Kagan⁵⁹, prefers an *s-cis* conformation when reacting with a diene. Approaching dienes favor a path from the face opposite of the large tolyl group **1.83** versus the sterically hindered facial pathway depicted by **1.84** (Figure 1.2). No explanation was given as to why **1.82** might prefer an *s-cis* conformation, although experimental results supported the theory.⁵⁹

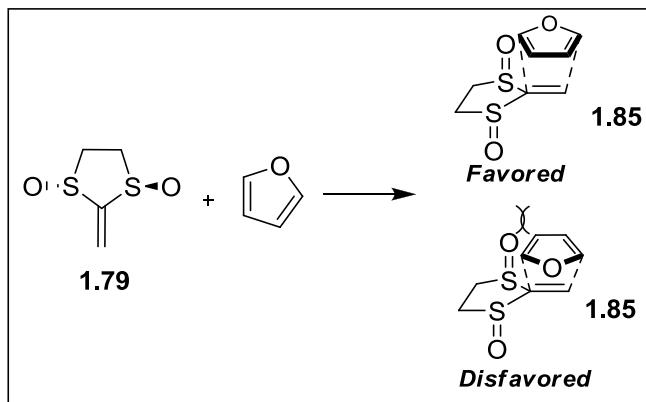
Figure 1.2: Diastereoselectivity model for Kagan's sulfoxonium salt **1.82**



The interpretation of the stereoselectivity of bis-sulfoxide **1.79** is more straightforward. The stereochemical outcome of the [4+2] cycloaddition of **1.79** with furan can be rationalized by the two transition states **1.85** and **1.86**.⁵⁶ The disfavored

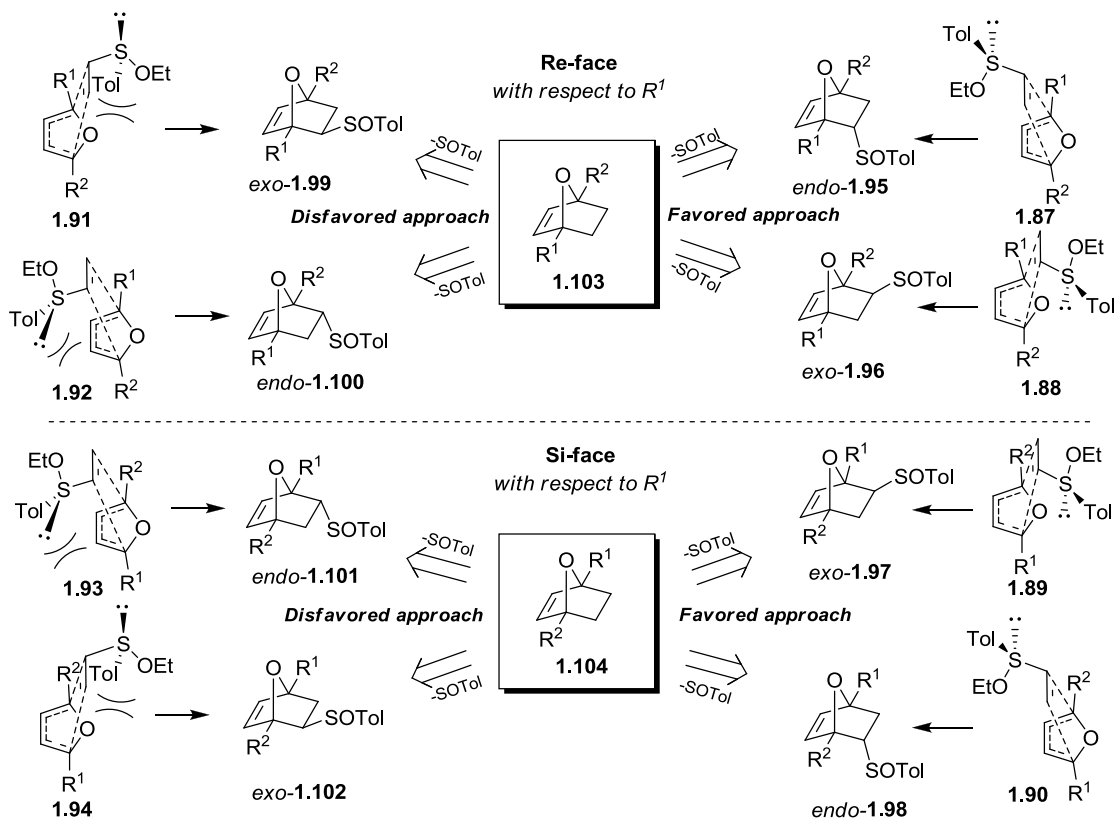
transition state **1.86** suffers from greater nonbonding interactions between the axial oxygen atom and the 3- and 4-positions of furan (Figure 1.3).

Figure 1.3: Selectivity model for Aggarwal's bis-sulfoxide **1.79**



The factors behind the stereoselectivity become increasingly complex once a more substituted diene is used as the reaction partner with **1.82** or **1.79**. As shown in Scheme 1.26, there are eight possible transition states (**1.87-1.94**) that lead to eight different possible products (**1.95-1.102**) when a 2,5-disubstituted furan is allowed to react with dienophile **1.82**. Transition states **1.87-1.90** are favored, assuming the approach of the diene is to the less hindered face of **1.82**, as opposed to transition states **1.91-1.94** where the diene approaches from the sterically crowded *p*-tolyl face of the dienophile.

Scheme 1.26: Possible facial approaches and products after desulfurization for **1.82**

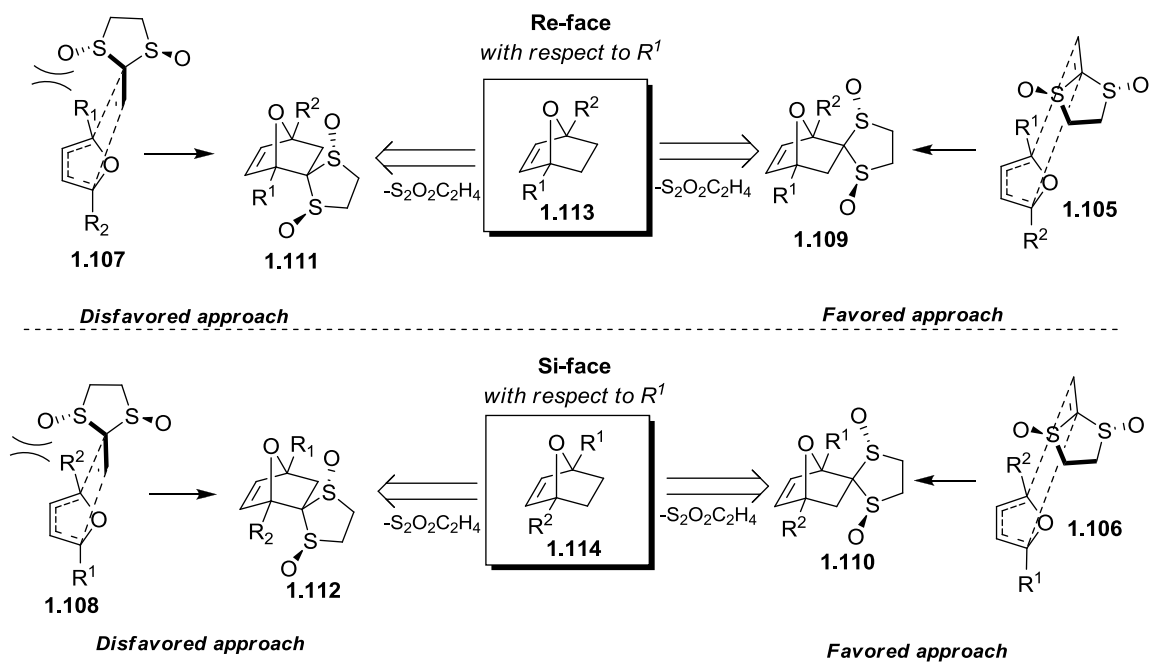


Because the carbon-sulfur bond will be cleaved after the cycloaddition only the facial selectivity is relevant to us. Cycloadducts **1.95**, **1.96**, **1.99**, and **1.100** all lead to final product **1.103** after desulfurization, because the vinyl sulfoxide approaches from the *re*-face of the diene. Likewise, desulfurization of substrates **1.97**, **1.98**, **1.101**, **1.102** would give oxabicyclic **1.104** because these substrates are formed by *si*-facial approach on the diene.

The number of possible products is halved by the Diels-Alder reaction of 2,5-disubstituted furans with dieneophile **1.79** since there are no *endo:exo* isomers. Of the four possible transition states **1.105**-**1.108** (Scheme 1.27), **1.105** and **1.106** are favored

based on Aggarwal's stereochemical model. Transition states **1.107** and **1.108** are disfavored due to nonbonding interactions of the 3- and 4- atoms of furan and the axial oxygen atom of the dieneophile. Desulfurization of substrates **1.109** and **1.111** would lead to oxabicyclic **1.113**. Similarly **1.110** and **1.112** would be transformed into **1.114** upon cleavage of the carbon sulfur bonds.

Scheme 1.27: Full map of facial approaches for **1.79** and result after desulfurization

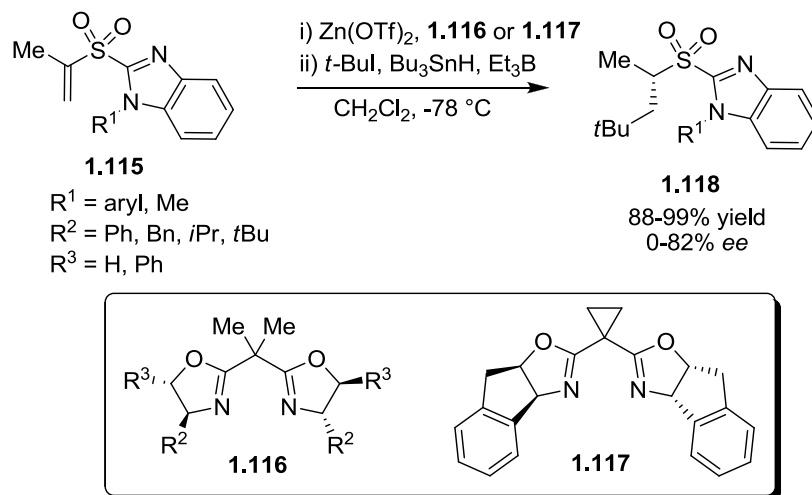


1.2.5. Background information related to the development of a chiral Lewis acid catalyzed cycloaddition with α,β -unsaturated sulfones.

If we were able to use a chiral Lewis acid to catalyze the cycloaddition between achiral starting materials, we could avoid the use of stoichiometric chiral auxiliary. To our knowledge, a chiral Lewis acid-directed, enantioselective Diels-Alder reaction between an achiral vinyl sulfone, sulfonamide, or sulfonate and furan has never been reported. Although this area is unsupported by direct precedent there have been reports of chiral Lewis acid mediated reactions involving similar vinyl sulfones and vinyl sulfonamides (*vide infra*).

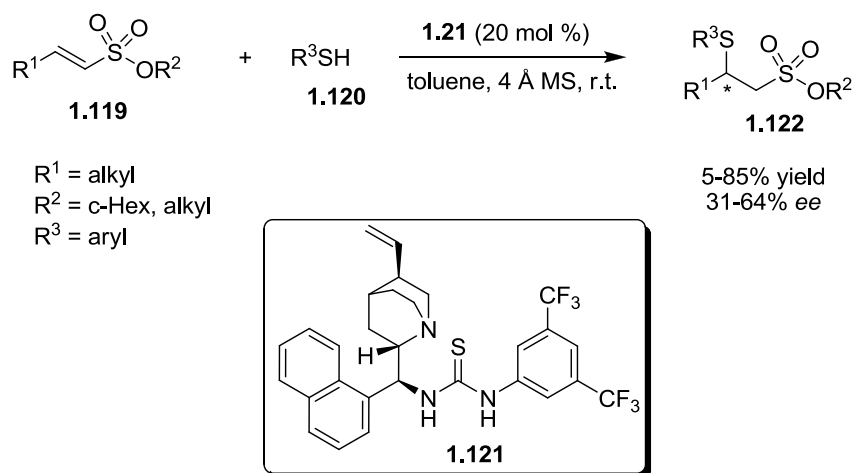
For example, Toru and co-workers, reported an enantioselective hydrogen atom transfer to α -sulfonyl radicals (Scheme 1.28).⁶² This reaction was controlled by the coordination of chiral Lewis acids to the sulfonyl oxygen atoms. The radical was generated by the addition of butyl-radical to the terminus of the double bond of **1.115**. The resulting α -sulfonyl radical was then quenched by hydride from the tin-hydride, presumably directed by the Lewis acid that was formed from zinc triflate and the chiral ligands **1.116** or **1.117**. The enantioenriched products **1.118** were obtained in good yields, but generally poor enantiomeric excesses were observed. Nevertheless, this example suggests that stereocontrol of vinyl sulfones may be possible with a chiral Lewis acid.

Scheme 1.28: Lewis acid directed addition-hydrogen atom transfer to sulfones



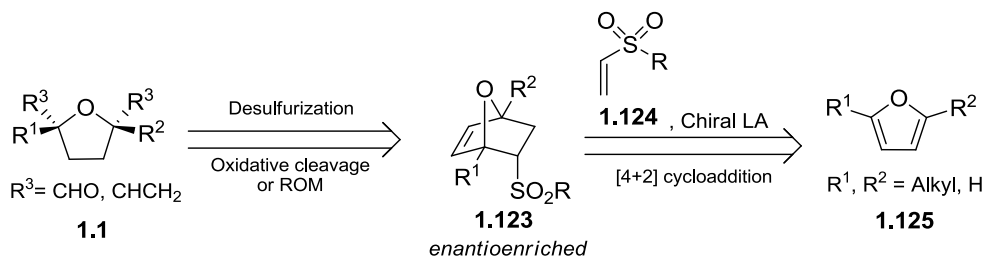
Enders and Hoffman also developed an enantioselective-organocatalytic Michael addition of sulfur nucleophiles to unsaturated sulfonates (Scheme 1.29).⁶³ Starting from a variety of achiral vinyl-sulfonates **1.119**, they added sulfur nucleophiles **1.20** to the β -carbon by activation with the bifunctional thiourea catalyst **1.121**. The yields and enantioenrichment of adduct **1.222** varied greatly, resulting in a method that lacks generality. However, this does represent an example of stereochemical induction using a chiral-organocatalyst to control the reactivity of a vinyl sulfonate.

Scheme 1.29: Organocatalytic asymmetric sulfur Michael additions to vinyl sulfonates.



Because of the available precedent suggesting that vinyl sulfones can undergo asymmetric reactions under chiral Lewis and Brønsted acid catalysis, we believed we might be able to establish conditions for an Lewis acid-catalyzed asymmetric intermolecular Diels-Alder between a vinyl sulfone and a furan. Accordingly, the 2,2,5-tri and 2,2,5,5-tetrasubstituted tetrahydrofurans **1.1** would be formed by the ring-opening of enantioenriched oxabicycle **1.123**, which would be generated by the asymmetric cycloaddition between achiral sulfone **1.124** and substituted-furan **1.125** (Scheme 1.30).

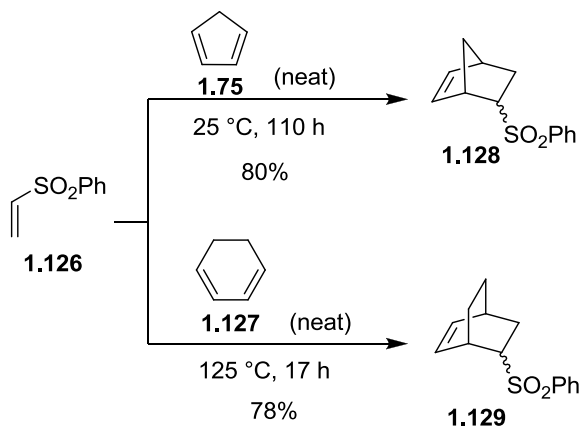
Scheme 1.30: Retrosynthesis of **1.1** using a chiral Lewis acid promoted cycloaddition



The first step in probing the feasibility of the plan would be to determine whether we could use a Lewis acid to catalyze the cycloaddition between substituted furan **1.125** and various vinyl sulfur derivatives of **1.124**. Once these conditions had been established, we would investigate the asymmetric reaction with chiral Lewis acids. Vinyl sulfones had previously been used as dienophiles in Diels-Alder reactions, but the use of catalysts or promoters to enhance the reaction had not been reported.

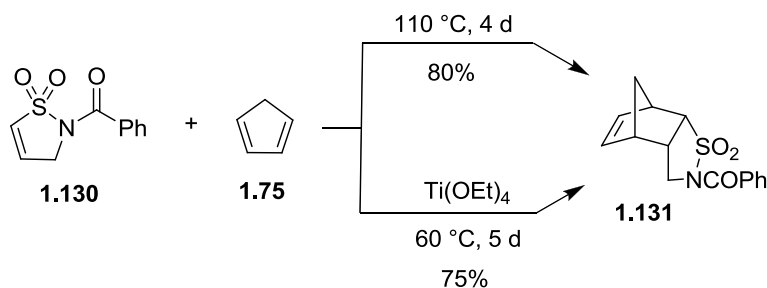
One example of a thermally promoted Diels-Alder reaction was published by Paquette and co-workers, who treated phenyl vinyl sulfone **1.126** with simple dienophiles, including cyclopentadiene (**1.75**) and cyclohexadiene (**1.127**), under somewhat forcing thermal conditions.⁵¹ The corresponding cycloadducts **1.128** and **1.129** were produced in good yields, but mixtures of *endo/exo* isomers (2:1) were obtained (Scheme 1.31). Discouragingly, however, he adds that “the generally available Lewis acid catalysts give no evidence of accelerating these reactions...”

Scheme 1.31: Paquette’s use of phenyl vinyl sulfone as a dienophile



Despite this claim, there was evidence that Lewis acids could indeed enhance the rate of Diels-Alder reactions with sulfone derivatives. Namely, Lee demonstrated that vinyl sultam **1.130** cyclized with dimethylfuran at high temperatures, forming cycloadduct **1.131** in good yield (Scheme 1.32).⁶⁴ When titanium tetraethoxide was added, the temperature required was significantly lower.

Scheme 1.32: example of a Lewis-acid catalyzed vinyl sulfonamide Diels-Alder reaction



There exists significant precedent to suggest that we might be able to catalyze an enantioselective cycloaddition between a vinyl sulfone or sulfonamide and furan. We set out to explore the feasibility of this transformation, modeling our reactions after the reported precedent (*vida supra*).

1.4. DEVELOPMENT OF THE ENANTIOSELECTIVE SYNTHESIS OF 2,2,5-TRI- AND 2,2,5,5-TETRASUBSTITUTED TETRAHYDROFURANS VIA [4 + 2] CYCLOADDITION AND RING-OPENING CROSS-METATHESIS

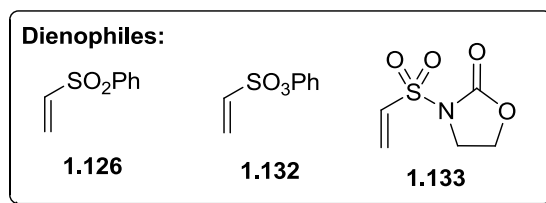
1.4.1. Development of the enantioselective Diels-Alder reaction

1.4.1.1. *Exploration of enantioselective cycloaddition with chiral Lewis acids*

As reported earlier, there is literature precedent for the use of a chiral auxiliary to direct an asymmetric cycloaddition between furan, and a dienophile with a cleavable activating group.^{56,59} While many of the aforementioned examples appeared to be promising starting points for our methodology (Schemes 1.23, 1.24 and 1.25), they all shared a single disadvantage; by using a sulfoxide or sulfonamide as the activating group it required a stoichiometric amount of chiral auxiliary. We thus sought to find a technique to perform an asymmetric [4+2] cycloaddition using achiral starting material, and a chiral Lewis acid. To accomplish this, we first aimed to find a suitable Lewis acid to catalyze the cycloaddition. After achieving this goal, we would then seek a chiral variant to achieve enantioselection.

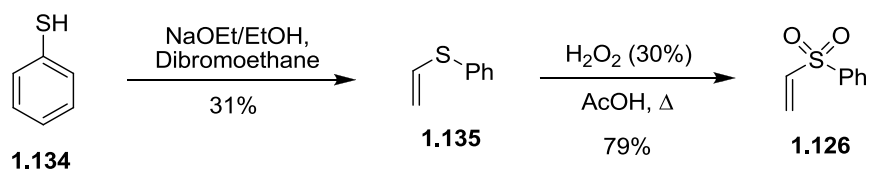
After a survey of the literature, we selected the three different unsaturated sulfur-activated dienophiles, vinyl sulfone **1.126**, vinyl sulfonate **1.132**, and vinyl sulfonamide **1.133**. Each of these olefins is either known to undergo [4+2] cycloadditions readily or is very similar to known reactive dienophiles (Figure 1.4).^{65,66}

Figure 1.4: Selected dienophiles for chiral Lewis acid study



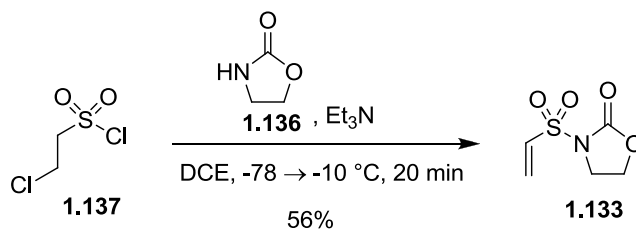
Phenylvinyl sulfone (**1.126**) was synthesized by the addition of thiolate **1.134** to dibromoethane to give vinyl sulfide **1.135** in 31% yield by a literature procedure (Scheme 1.33).⁶⁷ The procedure can easily be done on large scale and required only a simple distillation to isolate the pure product. The thioether **1.135** was then oxidized in the presence of an excess of hydrogen peroxide in acetic acid to give **1.126** in 79% yield. This route was not optimized as it was sufficient to produce enough **1.126** for our purposes.

Scheme 1.33: Synthesis of phenyl vinyl sulfone (**1.126**)



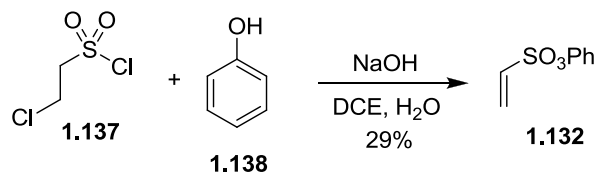
Dienophile **1.133** was synthesized by the addition of commercially available oxazolidinone **1.136** to chloroethane sulfonyl chloride (**1.137**) in the presence of triethylamine (Scheme 1.34).⁶⁸ The key to obtaining good yields in this reaction was a change in the order of addition, so **1.137** was added dropwise to **1.136** in the presence of base at low temperature, to give **1.133** in 56% yield.

Scheme 1.34: Synthesis of vinyl sulfonamide **1.133**



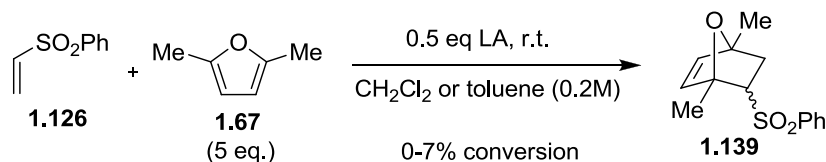
Vinyl sulfonate **1.132** was synthesized by a known procedure from chloroethane sulfonyl chloride (**1.137**) and phenol (**1.138**) (Scheme 1.35).⁶⁹

Scheme 1.35: Synthesis of vinyl sulfonate **1.132**



With dienophiles **1.126**, **1.132** and **1.133** in hand, the next task was to identify Lewis acids capable of catalyzing the [4+2] cycloaddition reaction. We first used phenyl vinyl sulfone (**1.126**), because it was well preceded to serve as an active Diels-Alder partner.⁶⁶ We added a wide variety of Lewis acids to a solution of sulfone **1.126** in the presence of 2,5-dimethylfuran (**1.67**) to screen for catalytic activity (Scheme 1.36). The Lewis acids shown in bold are those that promoted at least some reaction. Trimethylaluminum gave approximately 7% conversion as judged by ^1H NMR spectrum of the crude reaction mixture. Boron trifluoride diethyl etherate and other aluminum based Lewis acids were also capable of generating trace amounts of **1.139**, but these reactions were accompanied by the formation of numerous unidentified side products.

Scheme 1.36: Screening for Lewis acid catalysis

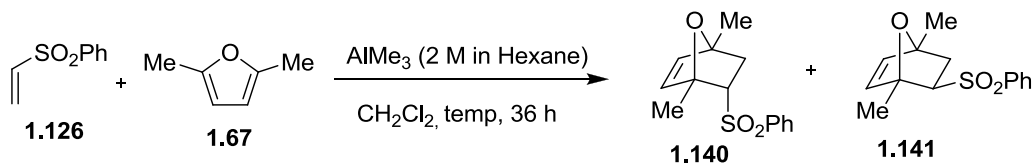


Lewis acids tested:

TiCl_4 , $\text{Ti}(\text{O}_i\text{Pr})_4$, $\text{Ti}(\text{OEt})_4$, ZnCl_2 (1M Et_2O), ZnI_2 , CuCl_2 , CuCl , $\text{Cu}(\text{OAc})_2$, CuI , **AlMe_3** , Al_iBu_3 , **Et_2AlCl** , **AlCl_3** , AlOTf_3 , **BF_3OEt_2** , $\text{Sc}(\text{OTf})_3$, FeCl_2 , $\text{Fe}(\text{III})\text{AcAc}$, $\text{Mg}(\text{NTf}_2)_2$, $\text{Al}(\text{NTf}_2)_3$

The trimethylaluminum-promoted reaction was then examined in more detail and optimized to see if synthetically useful yields could be obtained (Table 1.1). The relative equivalence of all reagents, reaction concentration, and temperature were varied, and we found that increasing the equivalents of dimethylfuran, the Lewis acid, and the reaction concentration all significantly improved the percent conversion. Lowering the temperature improved the *endo/exo* selectivity. Varying the solvent had little effect on the yield. The major *endo*-cycloadduct **1.140** was recrystallized, and its structure was proven by X-ray crystallography (Figure 1.5). The ratio of the *endo/exo*-cycloadducts was determined by integration of the proton alpha to the sulfone in the ^1H NMR spectrum of the purified mixture. The characteristic proton appears at δ 3.54 ppm for **1.140** and at δ 3.21 ppm for **1.141**.

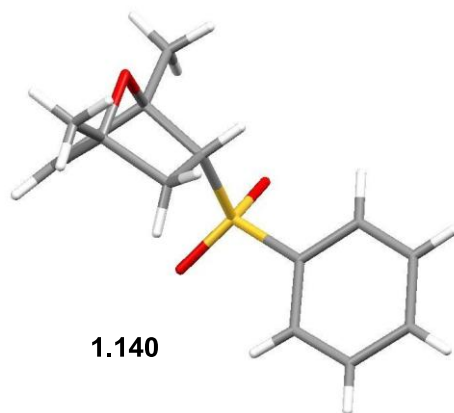
Table 1.1: Optimization of the trimethylaluminum promoted Diels-Alder reaction



Entry #	eq 1.126	^a AlMe_3 eq	Furan eq	Conc. (M)	temp (°C)	^b Conversion (%)	^c endo 1.140	^c exo 1.141
1	1.0	0.2	5.0	0.12	25	trace	-	-
2	1.0	0.5	5.0	0.12	25	7	1.00	0.22
3	1.0	1.0	5.0	0.12	25	27	1.00	0.11
4	1.0	2.0	5.0	0.12	25	69	1.00	0.21
5	1.0	2.0	20.0	0.12	25	81	1.00	0.20
6	5.0	2.0	1.0	0.4	25	4	-	-
7	1.0	2.0	5.0	0.6	25	89	1.00	0.27
8	1.0	2.0	5.0	0.6	5	95	1.00	0.13
9	1.0	2.0	5.0	0.6	-20	18	1.00	0.27

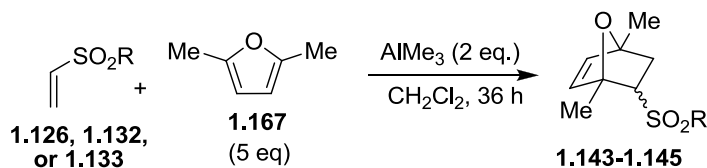
All reactions run for 36 h in anhydrous CH_2Cl_2 . ^a AlMe_3 added as a 2 M solution in hexane. ^bPercent conversion measured by ¹H NMR integration. ^cRatio measured by ¹H NMR integration. Other solvents screened: hexanes, CH_3CN , DMF, Et_2O , THF, MeOH, dioxane, chlorobenzene, xylenes, pyridine, toluene, $\text{ClCH}_2\text{CH}_2\text{Cl}$, EtOAc, CHCl_3 .

Figure 1.5: Crystal structure of major *endo*-cycloadduct **1.140**



With these results in hand, we applied the same conditions to the other dienophiles **1.132** and **1.133** (Table 1.2). We found that we were able to catalyze each reaction with dimethyl furan **1.67** in acceptable yield, giving the respective cycloadducts **1.143**, **1.144**, **1.145** in 62-95% conversion by analysis of the ^1H NMR spectrum of the crude reaction mixture. *The results represent the first Lewis acid catalyzed Diels-Alder reaction between furans and a vinyl sulfone, sulfonate, or sulfonamide.*

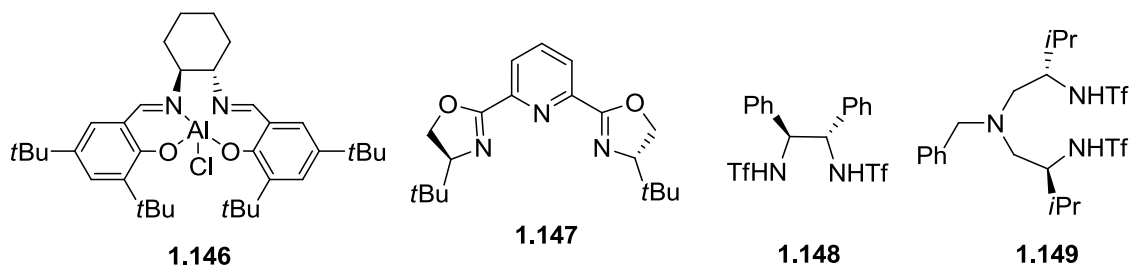
Table 1.2: Application of the trimethylaluminum conditions to **1.126**, **1.132**, and **1.133**



-R	temp.	conversion	product
Ph	5 °C	95%	1.143
OPh	25 °C	65%	1.144
N-C(=O)-CH2-CH2	25 °C	62%	1.145

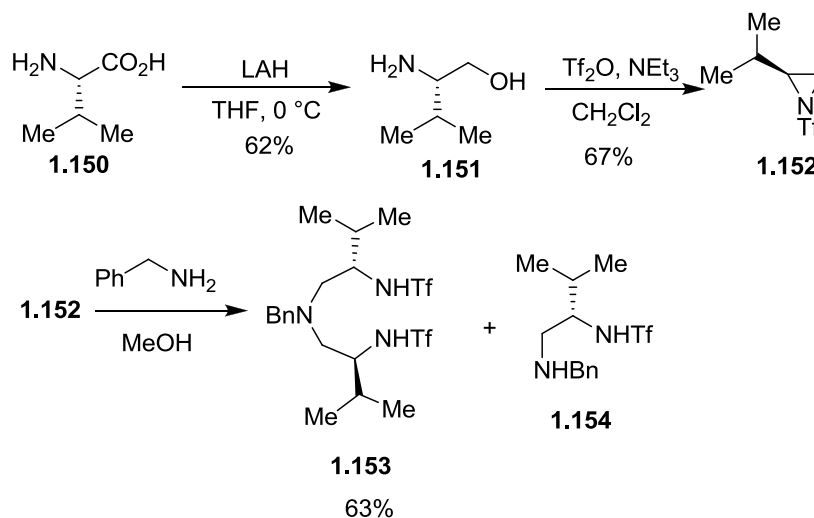
Having found conditions to promote the cycloaddition of each dienophile with furan **1.167**, we examined the series of chiral ligands **1.146-1.149** that might be used to pair with aluminum Lewis-acids (Figure 1.6). Ligands **1.147-1.148** and Lewis acid **1.146** were already on-hand, and ligand **1.149** was synthesized according to a known literature procedure.⁷⁰ Lewis acid **1.146** came pre-prepared with the aluminum metal center, whereas ligands **1.147**, **1.148**, and **1.149** needed to be premixed with an aluminum Lewis acid to form the active catalyst.

Figure 1.6: The collection of ligands or Lewis-acids to be screened in the cycloaddition



Chiral ligand **1.149** was prepared from (L)-valine (**1.150**) *via* the three-step sequence shown in Scheme 1.37.⁷⁰ The reduction of **1.150** to alcohol **1.151** was performed using LiAlH_4 ,⁷¹ and the aziridine **1.152** was prepared from **1.151** *via* an intramolecular displacement and used without purification. Ring-opening of **1.152** with benzylamine gave the desired ligand **1.153** along with side product **1.154**, which was not reported in the literature. Compound **1.154** was characterized by analysis of ^1H NMR and ^{13}C NMR spectra.

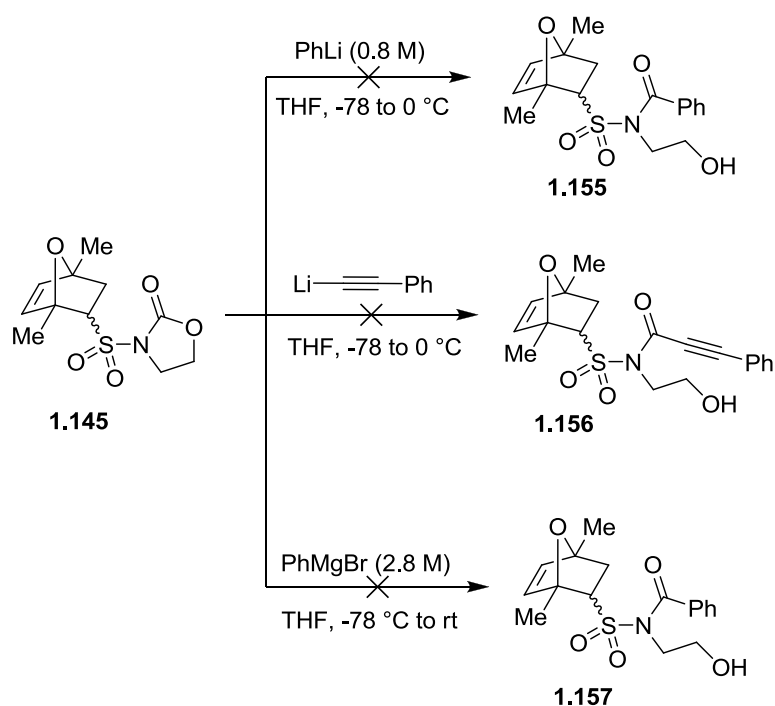
Scheme 1.37: Preparation of valine derived chiral ligand **1.153**



Before we could begin a full chiral Lewis acid screening, we prepared racemic samples of cycloadducts **1.143-1.145** in order to develop HPLC methods to determine enantiomeric excesses. When working with cycloadduct **1.145**, we quickly realized that we could not detect its isomers using HPLC UV absorbance detectors, this made it very difficult to purify **1.145**, and impossible to determine the enantiomeric excess. In an

effort to append a UV active group onto **1.145**, we attempted to ring-open the oxazolidinone ring of **1.145** with aromatic nucleophiles (Scheme 1.38). Despite some precedent for this reaction, no trace of any of desired products **1.155**, **1.156**, or **1.157** was ever detected.⁷²

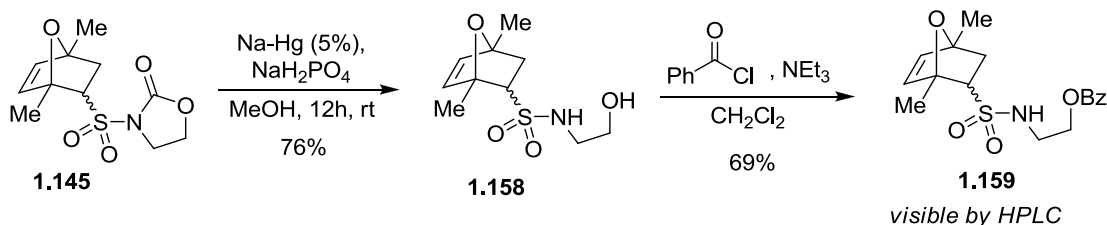
Scheme 1.38: Failed attempts to derivatize **1.145** for HPLC studies



As a result of some related work, we found that the oxazolidinone of oxabicyclic **1.145** could be decarbonylated into alcohol **1.158** 76% yield upon exposure to sodium-mercury amalgam in methanol. The free hydroxyl group of **1.158** was then benzoylated using benzoyl chloride and triethylamine to give UV-active compound **1.159** in 69%

yield (Scheme 1.39). This method would enable us to determine the enantioenrichment of cycloadduct **1.145**.

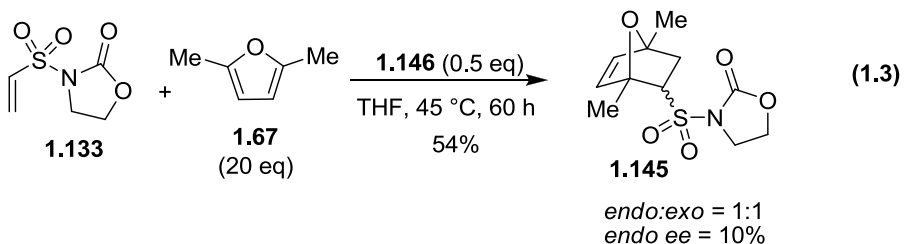
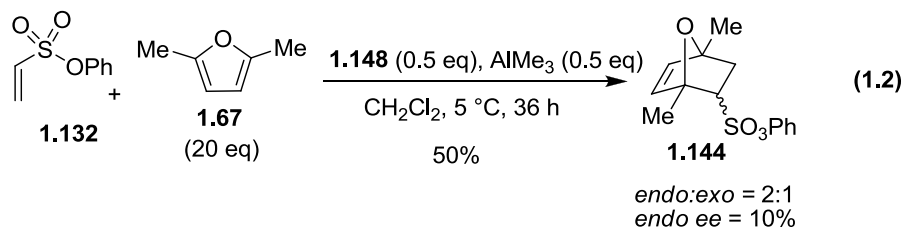
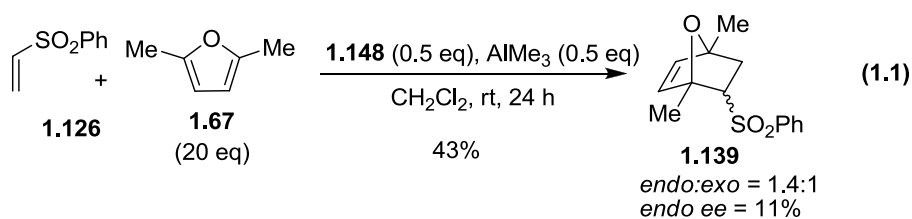
Scheme 1.39: Method for derivatization of **1.145**, leading to visibility by HPLC detectors



Chiral Lewis acid **1.146** and chiral ligands **1.147-1.149** were screened in the [4+2] cycloaddition between dimethylfuran **1.67** and vinyl sulfone **1.126** (equation 1.1), vinyl sulfonate **1.132** (equation 1.2), and vinyl sulfonamide **1.133** (equation 1.3). The yields and selectivities varied from poor to moderate under each set of circumstances; below is a summary of the best of those results for olefins **1.126**, **1.132**, and **1.133**.

Enantioselective Diels alder of the vinyl sulfone **1.126** with **1.67** worked optimally when promoted by bis-triflamide ligand **1.148** complexed with trimethylaluminum to give a 43% yield of cycloadduct **1.139** as a ratio (1.4:1.0) of *endo:exo* isomers as determined by analysis of the ¹H NMR spectrum of the purified cycloadduct (equation 1.1). However, the enantiomeric excess, was only 11% for the major *endo*-isomer. Similarly, vinyl sulfonate **1.132** reacted with dimethylfuran **1.67** in the presence of ligand **1.148** and trimethylaluminum, to give 50% yield of **1.44** as a mixture (2:1) of *endo/exo*-isomers by analysis of the ¹H NMR spectrum of the purified cycloadduct (equation 1.2), with the characteristic protons alpha to the sulfonate appearing at 3.75 ppm and 3.38 ppm. However, the enantiomeric excess was only 10%

for the major isomer. Finally, the best conditions for the Diels-Alder cycloaddition of sulfonamide **1.135** involved using precomplexed ligand **1.146**, to give cycloadduct **1.145** in 54% yield as a mixture (1:1) of *endo*- and *exo*-isomers by analysis of the ^1H NMR spectrum, with the characteristic protons alpha to the sulfonamide appearing at 2.26 ppm and 2.01 ppm. Unfortunately, the enantiomeric excess of the major isomer was also only 10% for both isomers.



While the preceding reactions represent the first examples of an enantioselective Diels-Alder cycloaddition of a vinyl sulfone with a furan that was promoted by chiral Lewis acid catalysis, they did not proceed with sufficiently high enantiomeric excess or

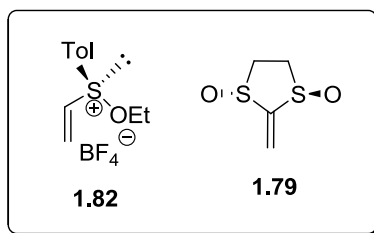
acceptable catalyst loadings to be synthetically useful. Accordingly, we are no longer exploring chiral Lewis-acid mediated cycloadditions of this type.

1.4.1.2. Exploration of diastereoselective cycloaddition with chiral vinyl sulfoxide 1.82

With the failure of the exploratory survey of chiral Lewis acid mediated cycloadditions of vinyl sulfone derivatives with furan, we turned our attention towards a more precedented technology. We focused on two promising methodologies: Aggarwal's chiral bis-sulfoxide **1.79** (Scheme 1.24), and Kagan's highly reactive chiral vinyl sulfoxide **1.81** (Scheme 1.25). Several questions stood out when assessing whether these methodologies would be suitable for our needs. Firstly, will these methods work with substituted tetrahydrofurans? Secondly, can we improve upon the disadvantages of each technique to create a simple, effective, and versatile methodology?

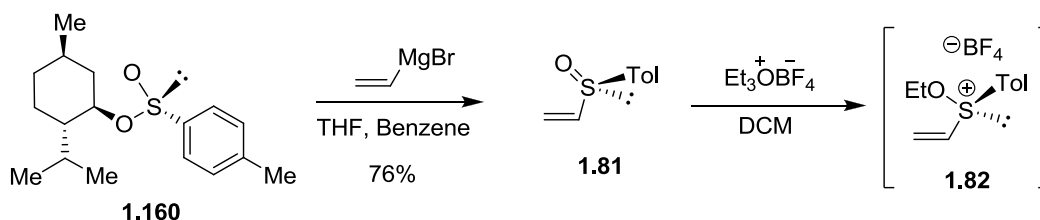
Based on our survey of the chemical literature, chiral sulfoxonium salt **1.82** and the bis-sulfoxide **1.79** became of interest to us due to their promising results (Schemes 1.24 and 1.25) with furan (Figure 1.7). Accordingly, screened dienophiles **1.82** and **1.79** for encouraging reactivity with 2,5-substituted furans, and to create a starting point for any improvements or developments needed for the methodology.

Figure 1.7: Kagan's sulfoxonium salt **1.82** and Aggarwal's chiral bis-sulfoxide **1.79**



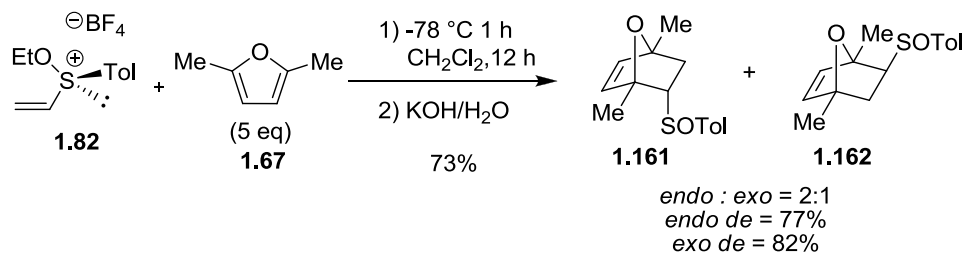
Dienophile **1.81** was prepared from (-)-(*1R*)-menthyl (*S*)-p-toluenesulfinate (**1.160**) by a procedure that was a modification of the literature report (Scheme 1.40).⁵⁸ Namely, it had been previously determined in the Martin group that the displacement of the menthyl group of **1.160** with freshly prepared vinylmagnesium bromide to form **1.81** proceeded more smoothly in benzene rather than in ether as reported earlier.⁸ Finally, alkylation of **1.81** using ethyl Meerwein's reagent afforded **1.82**, which was directly used in the cycloaddition.

Scheme 1.40: Synthesis of chiral vinyl sulfoxide **1.81**, and activation by Meerwein's salt



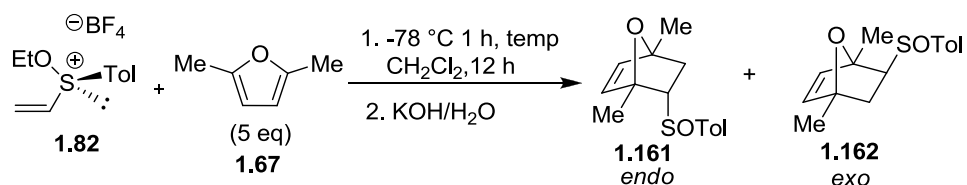
Initial screening of dienophile **1.82** began with using 2,5-dimethylfuran (**1.67**) as the cycloaddition partner, because it had previously been shown in the Martin lab to react with **1.82** in moderate yield (73%), *endo:exo* selectivity (2:1) of cycloadducts **1.161** and **1.162**, and π -facial selectivity (*endo d.e.* = 77%, *exo d.e.* = 82%) after some minor optimization (Scheme 1.41).⁸ The hope was that we could enhance these results and establish optimal conditions.

Scheme 1.41: Previously reported cycloaddition results in Martin lab⁸



Dienophile **1.82** was subjected to a number of conditions (Table 1.3) to determine the effects of temperature and solvent on the reaction. The diastereomeric excess (*de*) refers to the excess between the two possible *endo* adducts **1.161** or the ratio between the two possible *exo* adducts **1.162**, as determined by analysis of the ¹H NMR spectrum, with the characteristic protons alpha to the sulfoxide appearing at 3.19 ppm and 2.88 ppm, respectively. The absolute structural assignments of **1.161** and **1.162** were confirmed by X-ray crystallography (Figure 1.8).

Table 1.3: Screening of variables to find optimal reaction conditions



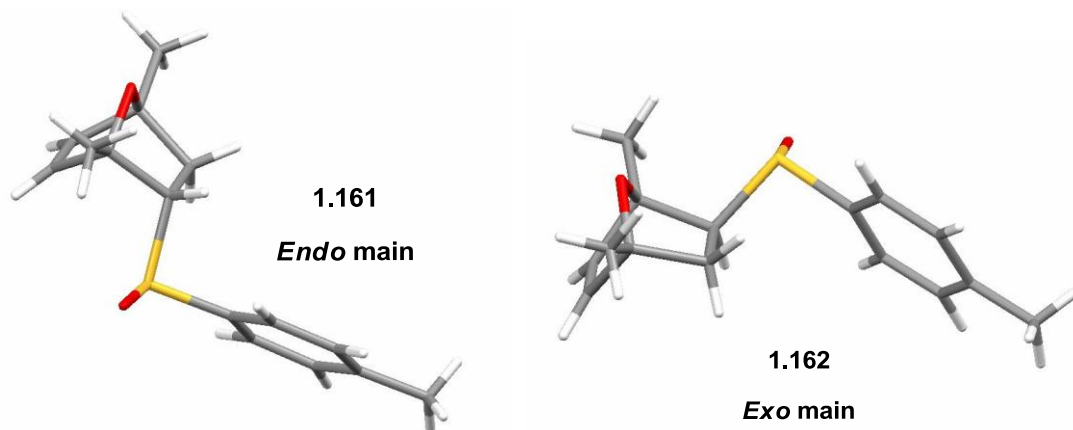
Entry	Solvent	Time (h)	Temp ($^\circ\text{C}$) ^f	Yield (%) ^a	de endo (%) ^a	de exo (%) ^a	1.161:1.162 ^a
1	CH_3CN	12	-20	65%	87	68	4:1
2	CH_2Cl_2	12	-20	>95%	90	84	5:1
3^b	EtOAc	12	-20	40%	n/a	n/a	n/a
4^b	Toluene	12	-20	50%	n/a	n/a	3:1
5^b	CHCl_3	12	-20	<10%	90	n/a	5:1
6	CH_2Cl_2	48	-20	>95%	90	84	5:1
7^c	CH_2Cl_2	12	-78	<5%	n/a	n/a	n/a
8	CH_2Cl_2	12	-40	54%	82	77	3:1
10^d	CH_2Cl_2	12	0	>90	80	85	2:1
11^d	CH_2Cl_2	12	25	>40%	n/a	n/a	n/a
12^e	CH_2Cl_2	12	50	0%	n/a	n/a	n/a

^aYields and diastereomeric excess calculated by NMR integration of characteristic protons of **1.81**, **1.161** and **1.162**.

^bUnidentified impurities in NMR did not allow for accurate integration of characteristic protons. ^cRecovered starting material, no detectable product ratios by NMR. ^dSignificant decomposition to a mixture of unidentified side products. Product appears to be mostly exo. ^eNo visible product or starting material via nmr.

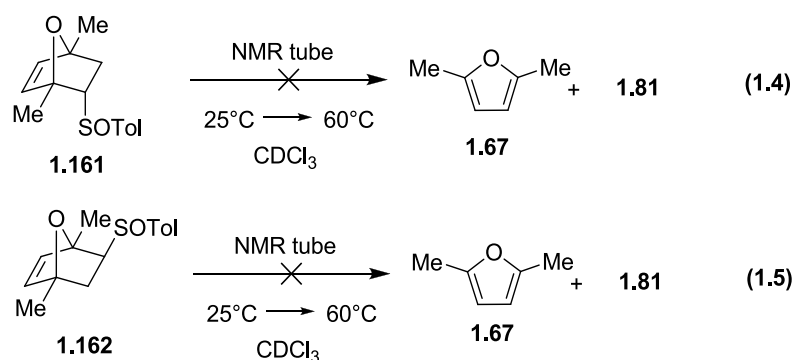
^fReaction stirred for 1 h at $-78\text{ }^\circ\text{C}$, then placed in an bath of the given temperature.

Figure 1.8: Crystal structures of the major *endo* and *exo* cycloadducts **1.161** and **1.162**.



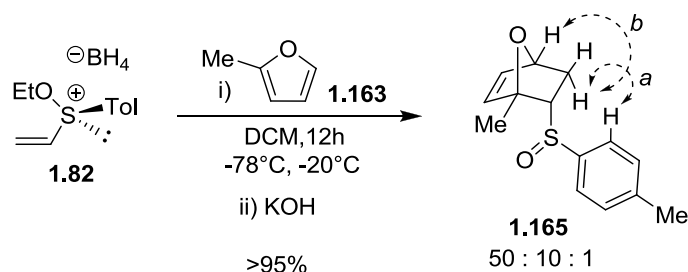
The results using dichloromethane as a solvent (Table 1.3, entry 2) were encouraging because they demonstrated that substitution on the 2- and 5-positions of furan actually have little or no effect on the selectivity of the reaction relative to those obtained with furan itself. While the diastereomeric excess and yield are very close to those reported by Kagan with furan (Scheme 1.25), the *endo:exo* ratio improved from 3:2 to 5:1. The improved selectivity probably occurred because the reaction was conducted at lower temperature than with furan. The greater reactivity of dimethylfuran can be attributed to higher HOMO levels than those of furan.⁷³

We were initially concerned that mild heating during the removal of solvent in the work-up procedure might cause a retro Diels-Alder that could either equilibrate the products or reduce yield. However, temperature studies in an NMR tube containing pure diastereomers of the main *endo*-product **1.161** and *exo*-product **1.162** showed no trace of reversibility up to 60 °C (equation 1.4 and 1.5).



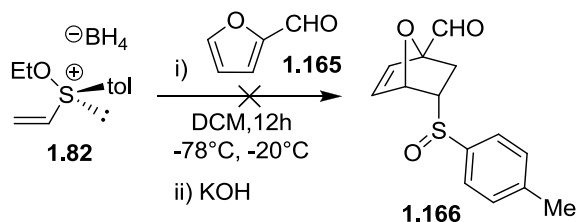
In an effort to expand the scope of the cycloaddition, 2-methylfuran (**1.163**) and 2-furaldehyde (**1.164**) were tested with dienophile **1.82**. The reaction of methylfuran **1.163** was comparable to that of 2,5-dimethyl furan, giving a ratio of three isomers of cycloadducts **1.165** in greater than 95% yield in a ratio of 50:10:1 by NMR (Scheme 1.42). All attempts to purify the individual diastereomers by reverse phase HPLC were unsuccessful. The main isomer was identified as the *endo* isomer based on the characteristic downfield shift of the proton alpha to the sulfoxide (δ 3.05 ppm). After some optimization, the main product was isolated by normal phase HPLC using a chiral ODH analytical column. The stereochemistry relative to the bridgehead methy group was determined by a distinct NOE coupling between the aromatic proton and the *endo* proton beta to the sulfur (*a*) along with the COESY and NOE coupling of the *endo*-proton to the equatorial bridgehead proton (*b*).

Scheme 1.42: Testing of dienophile **1.82** with 2-methylfuran



The electron deficient diene 2-furaldehyde (**1.165**) was unreactive with dienophile **1.82** and gave only recovered starting material (Scheme 1.43).

Scheme 1.43: Testing of dienophile **1.82** with 2-furaldehyde

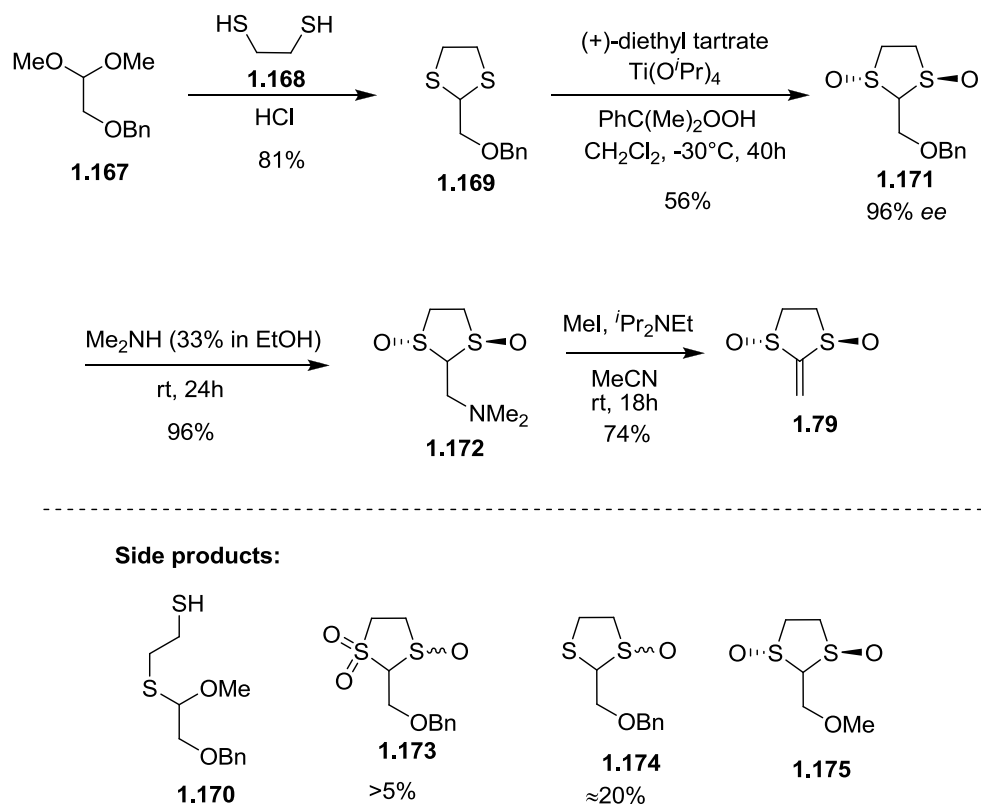


1.4.1.2. Diastereoselective cycloaddition with chiral bis-sulfoxide **1.79**

In order to determine the most suitable dienophile we synthesized **1.79** according to a known procedure (Scheme 1.44).⁷⁴ Accordingly, benzyloxyacetaldehyde dimethyl acetal (**1.67**) was converted to thioacetal **1.169** using ethanedithiol (**1.168**) and HCl. Although the original procedure required a chromatographic purification of **1.169**, we found this tedious step could be avoided by working up the reaction with multiple aqueous NaOH extractions of the organic layer to remove excess ethanedithiol (**1.168**)

and mixed S,O-acetal **1.170** from the reaction mixture. Diastereoselective oxidation of thioacetal **1.169** afforded **1.171** in 56% yield as compared to the 68% reported in the literature.⁷⁵ The enantiomeric excess was determined to be 96% by chiral HPLC. Some over-oxidized product **1.176** and mono-oxidized substrate **1.177** were isolated along with recovered starting material.

Scheme 1.44: Synthesis of Aggarwal's bis-sulfoxide **1.79**



The reported conditions for converting of **1.174** to the tertiary amine **1.175** used dimethylamine in acetonitrile; however, this is not commercially available and

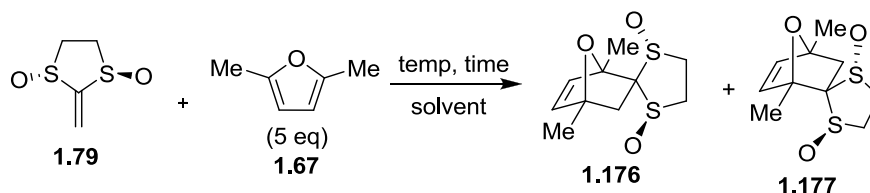
dimethylamine gas is prohibitively expensive. Conditions were screened using commercially available dimethylamine in a variety of solvents, and we eventually found that dimethylamine in ethanol (33%) gave **1.175** in 96% yield. The purification of **1.175** proved to be exceptionally difficult due to its high polarity and instability on silica gel. When **1.172** was purified by chromatography on silica in the presence of methanol, only methoxy-substituted product **1.175** was recovered. Various solvent systems on silica and neutral and basic alumina were tested, and eventually we found that using 100% acetone with 0.1% triethylamine on silica was found to be an acceptable chromatographic system for the purification of **1.172** without any detectable loss due to conjugate addition.

The Hoffman elimination to convert **1.172** to target dienophile **1.79** also led to a difficult purification step. The bis-sulfoxide **1.79** was reportedly purified by column chromatography with acetone. Surprisingly, these conditions led exclusively to the formation of a number of unidentified side products. Dienophile **1.79** appears to be sensitive to prolonged exposure to water, which prevented any aqueous workup of the reaction. The reaction mixture was thus concentrated, and crude **1.79** was isolated along with a large amount of ammonium salts. Some attempts to precipitate the salts from pentane/ether mixtures were mildly successful, giving **1.79** in $\approx 80\%$ purity. Column chromatography conditions were screened, and it was found that **1.79** could be isolated in good yield with minimal formation of unwanted side products by filtering the crude material through a short silica gel column with pure acetonitrile.

Similar to the reported reaction of **1.79** with furan, we found that **1.79** underwent facile cycloaddition with dimethylfuran (**1.67**) at room temperature. Although the reaction in dichloromethane gave slightly better diastereomeric excess (Table 1.4, entry 1) than other solvents, the reaction proceeded much faster in chloroform, perhaps due to

catalysis with residual acid (Table 1.4, entry 3). Chloroform was thus chosen as the optimal solvent due to the assumption that the increased reactivity may allow us to perform the reaction at lower temperatures, thus hopefully achieving greater stereoselectivity. A number of Lewis acids were screened, tin tetrachloride and scandium triflate improved the diastereomeric excesses (Table 1.4, entries 8 and 9). Structures of **1.176** and **1.177** were assigned tentatively based on a further downfield shift of the protons beta to the sulfoxides at δ 2.60 ppm for **1.176**, versus δ 2.39 ppm for **1.177**. However, determination of the structures has not been achieved. Although the cycloaddition proceeds cleanly and in high yield, separation conditions for **1.176** and **1.177** have not been developed.

Table 1.4: Screening of dienophile **1.79** with dimethyl furan under various conditions

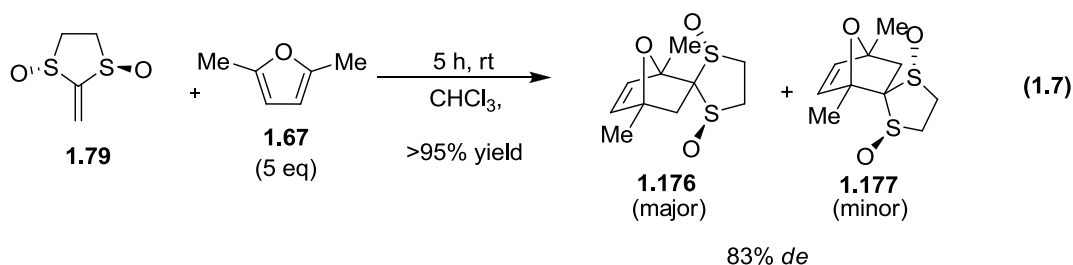
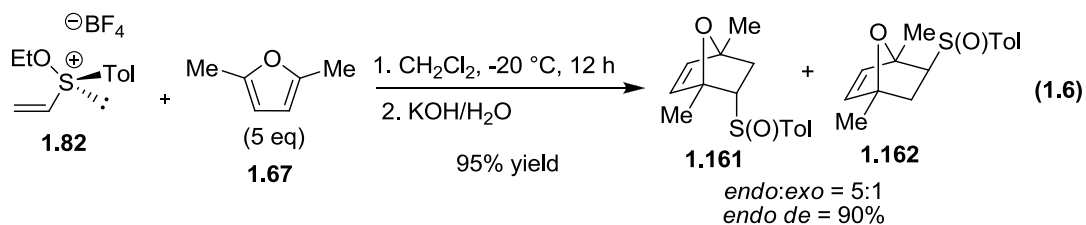


Entry	Solvent	Time (h)	Temp (°C)	Yield (%) ^a	de (%) ^a	Additive ^b
1	CH ₂ Cl ₂	12	25	88	86	none
2	CH ₃ CN	50	25	86	81	none
3	CHCl ₃	5	25	>95	83	none
4	CHCl ₃	12	-20	17	82	none
5	CHCl ₃	12	0	49	82	none
6 ^c	CHCl ₃	10	50	54	87	none
7	CHCl ₃	12	25	70	82	ZnCl ₂
8	CHCl ₃	12	25	64	89	Sc(OTf) ₃
9 ^d	CH ₃ CN	8	-78	n/a	90	SnCl ₄
10	CH ₃ CN	8	-78	30	74	BF ₃ OEt

^aYields and diastereomeric excess calculated by NMR integration of the characteristic protons beta to the sulfoxide. ^b1 eq of additive. ^cCrude mixture contained significant decomposed material. ^dUnidentified impurities in NMR did not allow for accurate integration of characteristic protons.

A summary of the best results from the early development work with tolyl vinyl sulfoxide **1.81** and chiral bis-sulfoxide **1.79** are summarized in equations 1.6 and 1.7. Activated vinyl sulfoxide **1.82** reacted with dimethylfuran **1.67**, giving a mixture (5:1) of cycloadducts **1.161** and **1.162** in 95% yield (equation 1.7). The major product was *endo*-adduct **1.161**, and it was determined to have a diastereomeric excess of 90% by HPLC.

Bis-sulfoxide **1.79** reacted with **1.67**, without the need for a promoter at room temperature, giving diastereomer **1.176** in 83% diastereomeric excess over and **1.177**.



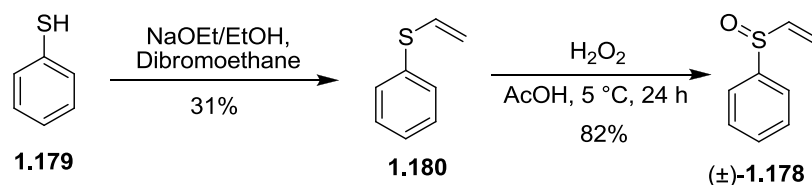
Both of these results were promising, and we hoped to use one of these dienophiles as the starting point for developing our new methodology. When examining equation 1.6 and equation 1.7, we decided to pursue the adaptation of chiral vinyl sulfoxonium salt **1.82**, and discontinue explorations using bis-sulfoxide **1.79**. This decision was made because the synthesis of **1.79** was long and problematic due to the many difficulties encountered during purification and scale-up. Additionally, the separation and visualization of adducts **1.176** and **1.177** was quite difficult by both HPLC and traditional flash chromatography.

1.4.1.3. Improvement and optimization of the cycloaddition

Based upon our results with the vinyl sulfoxide **1.81**, we concluded that there were several shortcomings that needed to be overcome. We wanted to eliminate the additional step to form the sulfoxonium salt **1.82** from the sulfoxide **1.81** (Scheme 1.25), perhaps using a Lewis acid instead of Meerwein's salt as an activator. Secondly, we wanted to reduce the furan loading as this is important when this methodology is applied to more substituted furans. For example, a high furan loading would lead to an inefficient route in the context of our ongoing total synthesis of coristatin A.⁸ Lastly, we wanted to improve the yield, *endo:exo* ratio, and enantioselectivity.

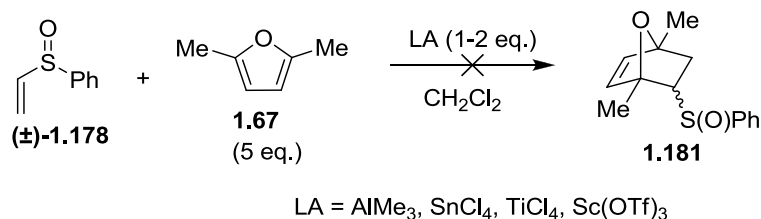
In an effort to avoid using ethyl Meerwein's salt to form a sulfoxonium salt **1.81**, we explored the possibility of a Lewis acid catalyzed reaction. We decided to use racemic vinyl sulfoxide **1.178** in order to screen cycloaddition conditions. To this end, racemic vinyl sulfoxide **1.79** was synthesized from thiophenol (**1.179**) and dibromoethane to give **1.180** in 31% yield (Scheme 1.45). Compound **1.180** was distilled from the reaction mixture and used directly in the oxidation with hydrogen peroxide to give racemic **1.178** in good yield along with trace over-oxidized phenyl vinyl sulfone. It should be noted that phenyl vinyl sulfoxide (**1.178**) was prepared for our model system based on the availability of starting materials.

Scheme 1.45: Preparation of phenyl vinyl sulfoxide for catalyst screening



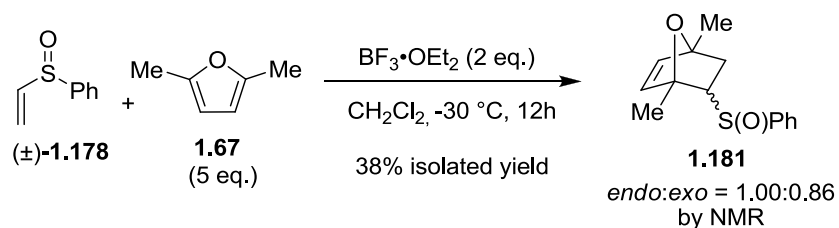
We explored Lewis acid-catalyzed reactions of **1.178** with dimethylfuran **1.67**. Use of AlMe_3 , SnCl_4 , TiCl_4 , and $\text{Sc}(\text{OTf})_3$ failed to give any detectable amount of desired cycloadduct **1.181** (Scheme 1.46).

Scheme 1.46: Failed Lewis acid screening for phenyl vinyl sulfone Diels-Alder



However, we discovered that BF_3OEt_2 promoted the cycloaddition between **1.178** and **1.67** giving **1.181** in 38% yield as a mixture (1.00:0.86) of *endo* and *exo* isomers (Scheme 1.47). The *endo:exo* ratio was determined by integration of the characteristic protons alpha to the sulfoxide by ^1H NMR, with the *endo* isomer appearing at δ 3.05 ppm and the *exo* isomer at δ 2.81 ppm.

Scheme 1.47: First successful Lewis acid catalysis with $\text{BF}_3 \cdot \text{OEt}_2$



When the Lewis-acid was switched to TMSOTf, **1.178** underwent cycloaddition with dimethylfuran to give **1.67** in good yield (Scheme 1.48). The stereochemistry of cycloadduct **1.181** was determined to be solely the *endo* isomer by analysis of the ^1H NMR spectrum of the purified cycloadducts. The structure of **1.181** was confirmed by X-ray crystallography (Figure 1.9). As the number of equivalents of TMSOTf was dropped from two to one-half, the yield dropped from 73% to 49%.

Scheme 1.48: Successful promotion of the cyclization using TMSOTf

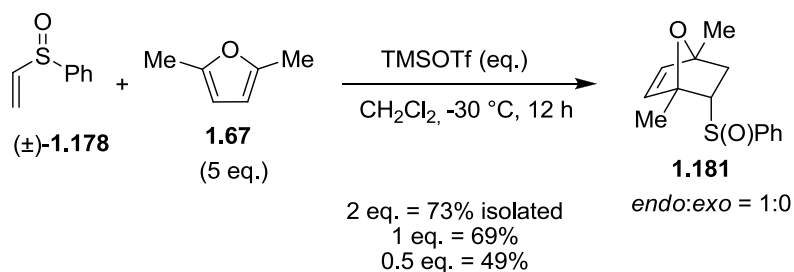
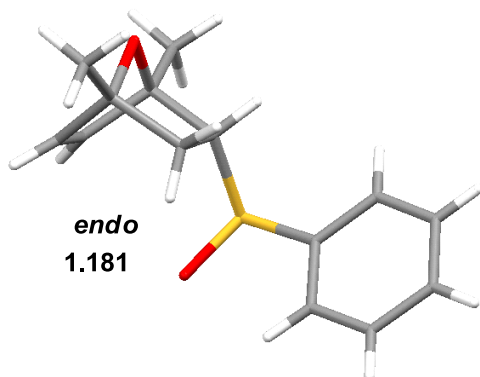
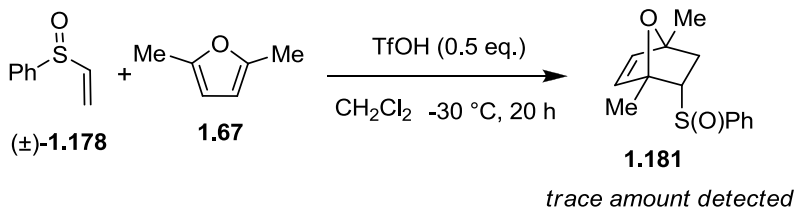


Figure 1.9: Crystal structure of *endo* cycloadduct **1.181**



A control reaction was performed to determine whether the reaction was catalyzed by trace amounts of triflic acid (Scheme 1.49). Phenyl vinyl sulfoxide (**1.178**) was exposed to half an equivalent of triflic acid in the presence of dimethylfuran **1.67**. Because only a trace amount of **1.181** was observed, we concluded that the reactions were not catalyzed by Brønsted acid.

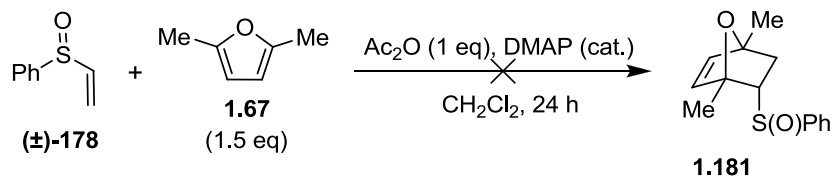
Scheme 1.49: Control experiment for triflic acid catalysis



In a related study, we examined whether other activating agents such as acylation reagents might be used to activate vinyl sulfoxide **1.178** using. When **1.178** was exposed

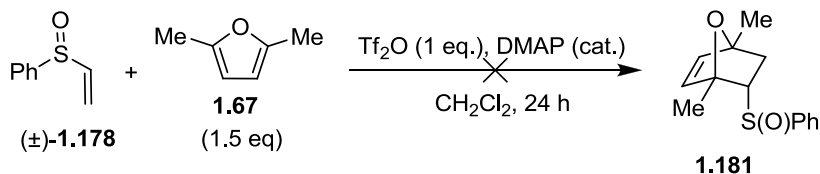
to acetic anhydride with a catalytic amount of DMAP in the presence of dimethylfuran **1.67** at room temperature, no reaction was observed by TLC (Scheme 1.50).

Scheme 1.50: Attempt to activate phenyl sulfoxide **1.178** with acetic anhydride



When triflic anhydride was used as an acylating agent the sulfoxide **1.178** decomposed rapidly, even at low temperatures (Scheme 1.51). No trace of cycloadduct **1.181** was detected. No further exploration into activation of the sulfoxide *via* acylation was done.

Scheme 1.51: Attempt to activate phenyl sulfoxide **1.178** with trifluoroacetic anhydride

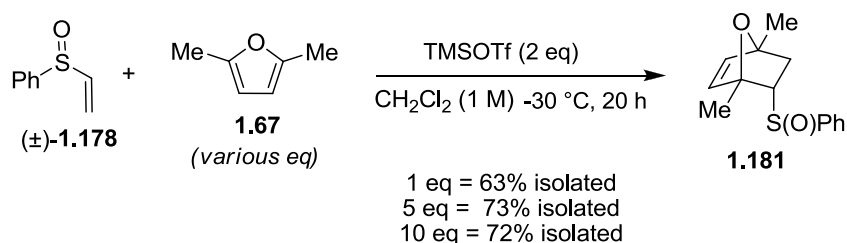


We then sought to optimize the conditions for the cycloaddition of **1.178**. Optimization began with an initial solvent screen with toluene, Et_2O , THF, hexane, CH_2Cl_2 , and CH_3CN . Of these solvents, the reaction worked in Et_2O and CH_3CN ; however, the rate was slower relative to dichloromethane. The effects of concentration

and temperature were then explored, and we found that higher concentrations improved the yield. Concentrations higher than 1 M tended to become too viscous or freeze at low temperatures. Temperatures lower than -30 °C made the reaction sluggish, and raising the temperature eroded the *endo:exo* ratio.

After we had found the optimal Lewis-acid, solvent, temperature, and concentration for the cycloaddition, we sought to lower the number of equivalents of furan (Scheme 1.52). The yield of **1.181** dropped only 10% when only one equivalent of dimethylfuran **1.67** was used, giving cycloadduct **1.181** in 63% yield. When ten equivalents of dimethylfuran was used, the yield remained essentially unchanged from when five equivalents were used, forming adduct **1.181** in 72% yield. Encouraged by the fact that yields were only slightly lower when using one equivalent of furan, we hoped that with further optimization, we might be able to lower the furan equivalence without a significant decrease in yield.

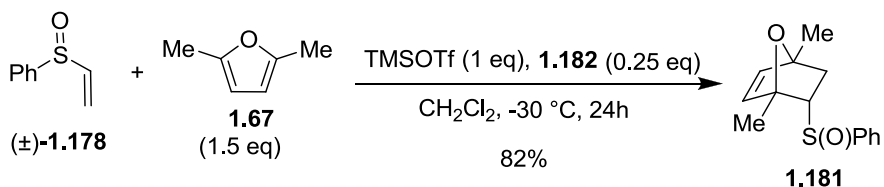
Scheme 1.52: Furan equivalence screening



The tendency of TMSOTf to hydrolyze rapidly in the presence of trace amounts of moisture led us to suspect that traces of protic acid may interfere with the reaction; perhaps by promoting polymerization of the furan. We hoped to eliminate this possibility

by adding hindered bases or water scavengers to the reaction and neutralize any residual acid present (Scheme 1.53). A number of additives were screened, including, 2,6-di-*tert*-butylpyridine (**1.182**), diisopropylethylamine, tetramethylpiperidine **1.183**, triethylamine, lutidine, NaH, molecular sieves, and proton sponge **1.184**. We found that 2,6-di-*tert*-butylpyridine (**1.182**) successfully limited the amount of polymerization of the furan and led to an improvement in the yield of **1.181** from 63% to 82%. The addition of this hindered base also allowed us to lower the TMSOTf loading from two to one equivalent.

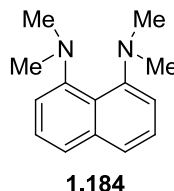
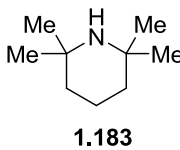
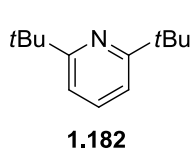
Scheme 1.53: Additives screening, and further optimization



Other additives screened:

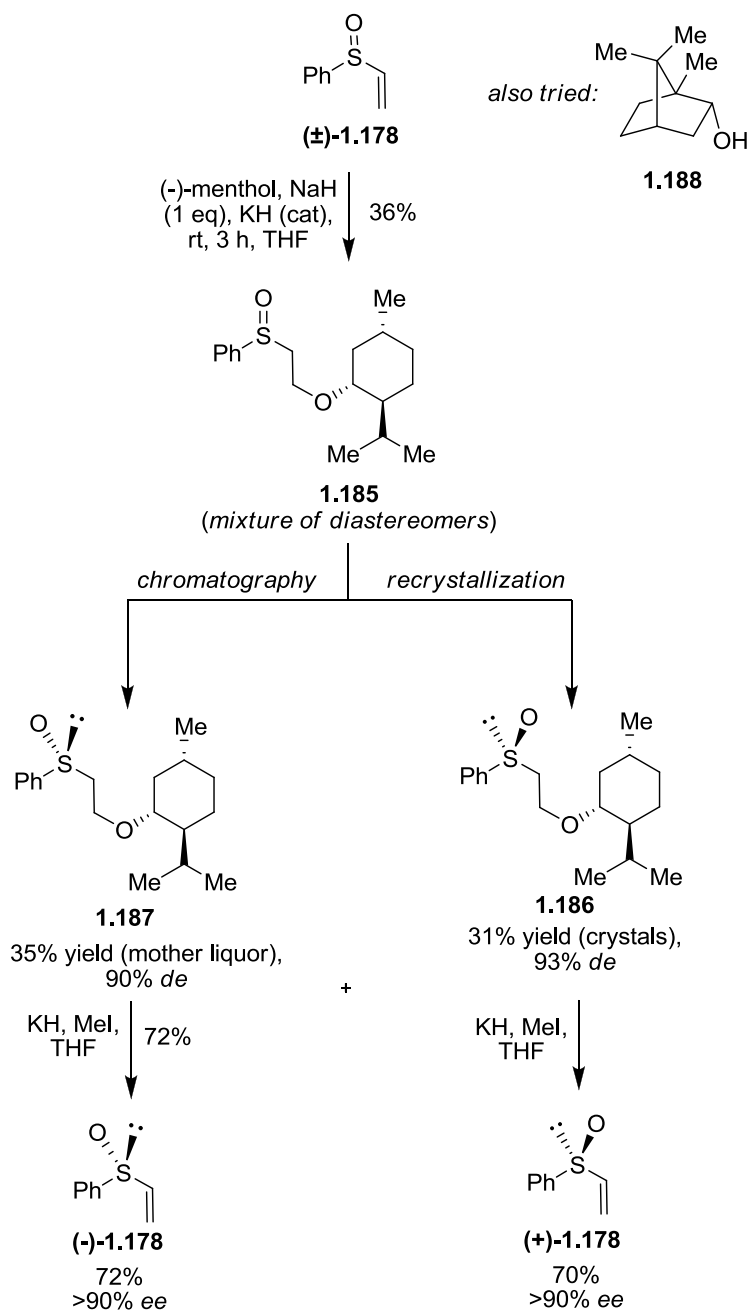
- DIPEA
- tetramethyl piperidine, **1.183**
- proton sponge, **1.184**
- TEA
- 2,6 Lutidine
- N-methyl imidazole
- NaH
- molecular sieves

Amine additives:



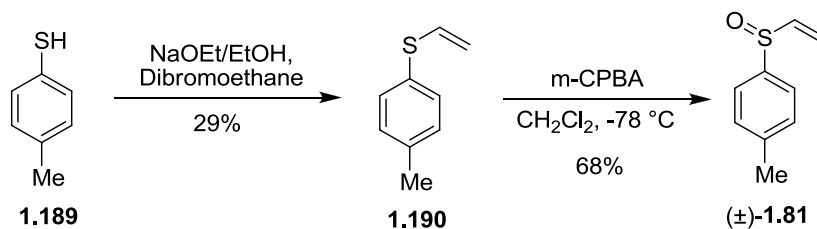
After successfully optimizing the cycloaddition of **1.67** with racemic phenyl vinyl sulfoxide (**1.178**), it was necessary to develop a procedure to synthesize **1.178** in enantiopure form. A procedure involving a diastereomeric resolution with (-)-menthol has been used to prepare *p*-tolyl vinyl sulfoxide (**1.81**),⁷⁶ and we adopted a similar procedure for the synthesis phenyl vinyl sulfoxide (**1.178**) (Scheme 1.54). Addition of (-)-menthol to racemic **1.178** gave a mixture (1:1) of diastereomers **1.185** in 36% yield (Scheme 1.56). This mixture was separated by repeated recrystallization from pentane at low temperature to give **1.186** in 31% yield and 93% diastereomeric excess and **1.187** in 35% yield and 90% diastereomeric excess. The double bond was then regenerated using potassium hydride in THF and methyl iodide to trap the mentholate. This led to the formation of pure vinyl sulfoxides (-)-**1.178** and (+)-**1.178**, both in 90% or greater enantiomeric excess as determined by HPLC. In an attempt to improve the diastereoselectivity, the same procedure was performed with (-)-borneol (**1.188**); however, all attempts to separate the resulting diastereomeric mixture failed

Scheme 1.54: Diastereomeric resolution of dienophile (\pm)-**1.178**



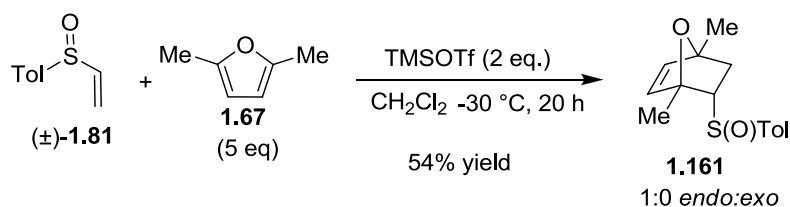
We wanted to confirm that that phenyl-substituted vinyl sulfoxide **1.178** was indeed a better dienophile for the cycloaddition than *p*-tol-substituted vinyl sulfoxide **1.81** under optimized conditions. In order to synthesize racemic **1.81** for the study, *p*-thiocresol (**1.189**) was deprotonated with NaOEt and then treated with dibromoethane; elimination occurred *in situ* to give **1.190** in 29% yield (Scheme 1.55). Thioether **1.190** could be distilled from the crude reaction mixture and used directly in the subsequent oxidation with *m*-CPBA to give racemic **1.81** in 68% yield after chromatography.

Scheme 1.55: Synthesis of racemic vinyl sulfoxide **1.81**



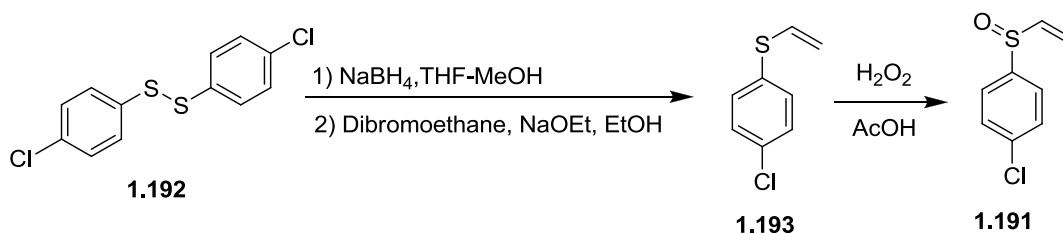
We then allowed (±)-**1.81** and dimethylfuran **1.67** to react in the presence of TMSOTf. The *endo* adduct **1.161** was isolated in 54% yield (Scheme 1.56). The structural assignment was based on the characteristic downfield ¹HNMR chemical shift of the proton alpha to the sulfoxide.

Scheme 1.56: Application of Lewis-acid catalyzed condition to tolyl sulfoxide **1.81**



We hypothesized that perhaps the electron donating character of the methyl group of **1.81** was responsible for the decreased yield relative to **1.178**. To probe the electronic effects chlorophenyl vinyl sulfoxide **1.191** was synthesized following the procedure outlined in Scheme 1.57. The disulfide **1.192** was reduced with NaBH_4 to give thiophenol⁷⁷ and then deprotonated with freshly prepared sodium ethoxide and treated with dibromoethane, elimination occurred *in situ* to give the vinyl sulfide **1.193**. Oxidation of the sulfide to sulfoxides with hydrogen peroxide in acetic acid gave the vinyl sulfoxide **1.191**.

Scheme 1.57: Synthesis of novel dienophiles with electron withdrawing aryl substituents



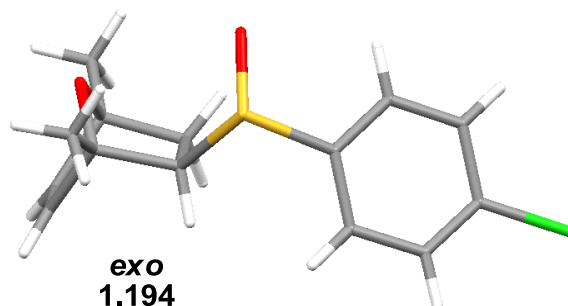
In order to compare the reactivity of all vinyl sulfoxides, **1.81**, **1.178**, and **1.191** were exposed to dimethylfuran **1.67** and TBSOTf (Table 1.5). Gratifyingly, the *p*-

chlorovinyl sulfoxide **1.191**, cyclized with dimethylfuran to give **1.194** in 98% yield as a mixture (20:1) of *endo:exo* adducts. The *endo:exo* ratio was determined by integrating the characteristic chemical shifts of the proton alpha to the sulfoxide. The *endo* isomer alpha proton appears at δ 3.39 ppm and the *exo* isomer at δ 2.75 ppm in the ^1H NMR spectrum. We believe that this increase in yield is likely a consequence of the lowering of the LUMO of the dienophile by the increased electron deficiency caused by changes in the orbital coefficients, which cause stronger secondary orbital interactions and a larger regiochemical preference.⁷⁸ The structure of the *exo* cycloadduct was determined by X-ray crystallography (Figure 1.10). Based on these results, we chose to develop **1.191** as the dienophile for our methodology.

Table 1.5: Trend in yield among the aryl vinyl sulfoxides

Ar=	isolated yield (%)	product	<i>endo</i> : <i>exo</i>	
1.81	68	1.161	20:1	
1.178	81	1.181	20:1	
1.191	94	1.194	20:1	

Figure 1.10: Crystal structure of *exo* cycloadduct **1.194**



We found that **1.191** reacted with furan (**1.46**) to give **1.195** in 99% yield, albeit with a lower *endo:exo* selectivity (1.6:1) (Scheme 1.58). The *endo:exo* ratio was determined by integrating the characteristic chemical shifts of the proton alpha to the sulfoxide. The *endo* isomer alpha proton appears at 3.69 ppm and the *exo* isomer at 3.11 ppm in the ^1H NMR spectrum. The structure of the major *endo* product was determined by X-ray crystallography (Figure 1.11). Furan proved to be very prone to polymerization even in the presence of base, so a large excess of furan was required.

Scheme 1.58: Improved dienophile **1.191** cycloaddition with furan

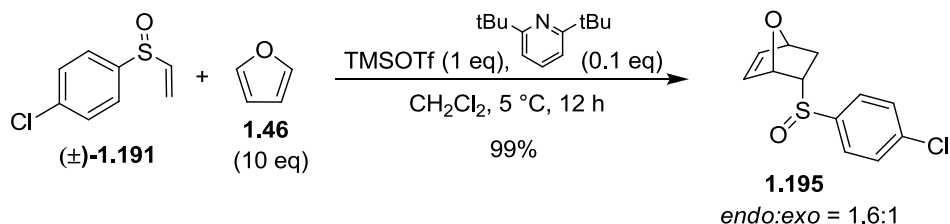
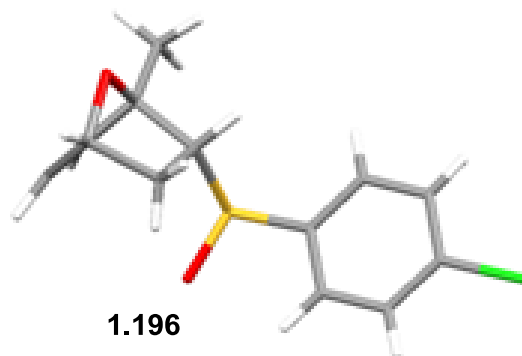


Figure 1.12: Crystal structure of endo-cycloadduct **1.196**



We sought to demonstrate that we could synthesize **1.191** enantioselectively. Following a procedure, similar to that used previously for **1.178**, we added (-)-menthol to **1.191** in a conjugate fashion giving a mixture (1:1) of diastereomers **1.197** and **1.98** in 81% yield (Scheme 1.60). After a single recrystallization, we obtained **1.197** in >95% diastereomeric excess by ^1H NMR spectroscopy and 37% yield. We obtained **1.197** in 35% yield after column chromatography of the mother liquor and in >95% diastereomeric excess by integration of the characteristic protons alpha to the sulfoxide in the ^1H NMR spectrum. The chemical shifts of the alpha protons for **1.197** appeared at 3.57 ppm and **1.198** at 3.76 ppm. The structure of **1.197** was determined by obtaining an X-ray crystallography (Figure 1.13). We also examined (-)-borneol (**1.188**) and (R,S)-*trans*-2-phenylcyclohexanol (**1.199**) and as potential resolving agents, but both gave inseparable mixtures of diastereomers.

Scheme 1.60: Diastereomeric resolution of dienophile (\pm)-**1.191**

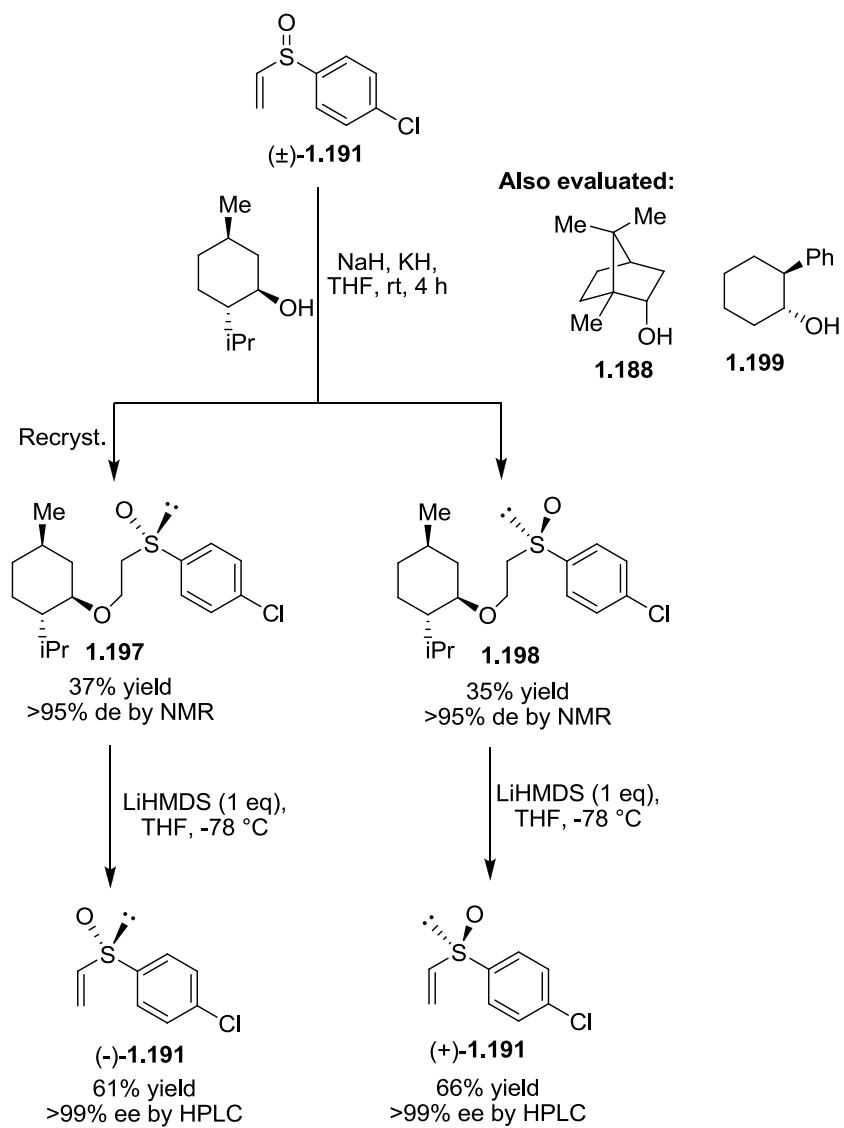
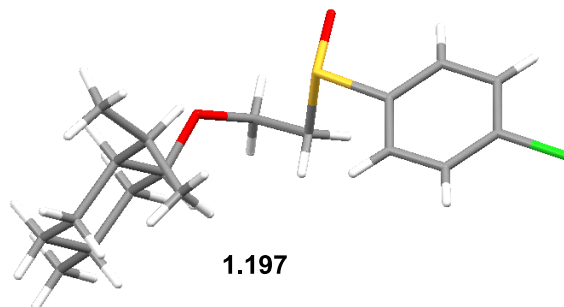


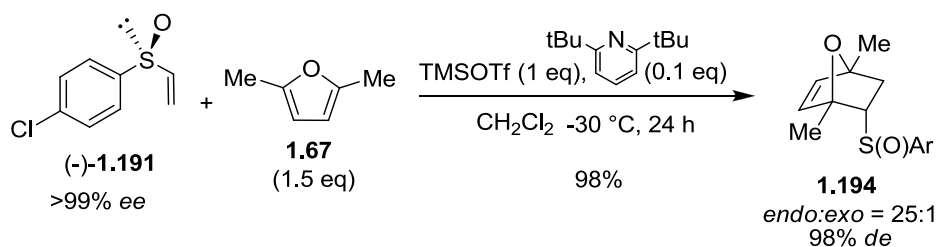
Figure 1.13: Crystal Structure of the recrystallized diastereomer **1.197**



With diastereomerically pure **1.197** and **1.198** in hand, we explored the elimination of the mentholate to give the desired enantiopure chiral vinyl sulfoxide **1.191**. Previously this type of elimination was done with KH in the presence of MeI, a procedure that unfortunately destroyed the mentholate.⁷⁶ These conditions gave **1.191** in 30% yield; but, before optimizing this procedure, we sought to develop conditions that would allow for the recovery of the menthol. We would thus further improve the utility of the method. After screening a number of bases, we found that freshly prepared LiHMDS was the optimal base for eliminating the mentholate, giving (-)-**1.191** in 61% yield and >99% enantiomeric excess by HPLC, and (+)-**1.191** in 66% yield and >99% enantiomeric excess by HPLC (Scheme 1.60).

All that remained was to determine the diastereoselectivity of the cycloaddition of **1.67** with enantiopure sulfoxide **1.191** under our optimized conditions. Chiral sulfoxide (-)-**1.191** thus underwent the Diels-Alder with dimethylfuran **1.67** to give **1.194** in 98% isolated yield and 98% diastereomeric excess by HPLC (Scheme 1.61).

Scheme 1.61: Highly stereoselective Diels-Alder reaction with **1.191**



We then needed to address the polymerization issue when using 2-methylfuran (**1.163**). We thus found that use of TBSOTf as the Lewis-acid avoided furan polymerization. In the case of 2-methylfuran (**1.163**), we were able to lower the furan loading from 30 to 2 equivalents (Table 1.6). This change improved the yield of the monosubstituted bicyclic sulfoxide **1.196** from 65% yield (Scheme 1.159) to 89% yield. In the cases of methylfuran **1.163** and dimethylfuran **1.67**, it was possible to use a substoichiometric amount of TBSOTf and still obtain high yield and diastereomeric excess. The use of one equivalent of Lewis acid was still required to obtain complete consumption of the sulfoxide in the case of furan (**1.46**). The yield and selectivities achieved when reacting **1.191** with furan (**1.46**) are better than those reported by Kagan using **1.81**; there was a 26% improvement in yield and a 19% increase in diastereomeric excess.⁵⁸ The final optimized yields and catalyst loadings are summarized in Table 1.6.

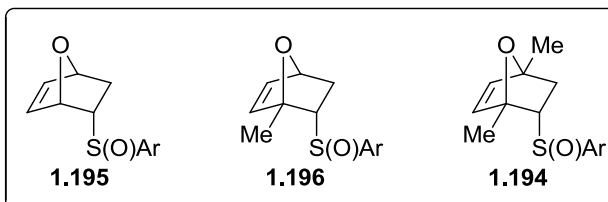
Table 1.6: Optimized cycloaddition conditions for all furans

(-)-1.191
Ar = 4-chlorophenyl

1.194-1.196

furan	product	L.A. eq.	furan eq.	temp. (°C)	yield (%)	endo:exo ^a	endo de (%) ^b
	1.195	1	5	0	98	1.8:1	88
	1.196	0.75	2	-30	89	25:1	99
	1.194	0.50	2	-30	94	25:1	98

^a determined by NMR. ^b determined by chiral HPLC.

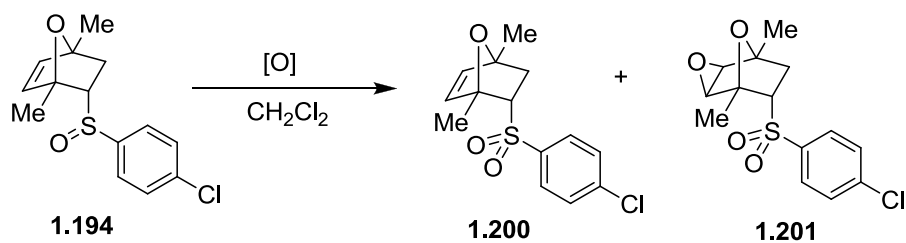


The Diels-Alder cycloaddition of **1.191** was thus developed to a satisfactory level, but, we would later find that the chemistry used to elaborate the oxabicyclic cycloadducts to the tetrahydrofurans **1.1** was more amenable to a sulfone moiety rather than the sulfoxide functionality (*vide infra*). Specifically, oxidative cleavage and ROCM of cycloadducts **1.194** and **1.196** was only viable with their sulfone analogues. We thus needed a way to oxidize the sulfoxide to the sulfone without affecting the yield or enantioselectivity. Moreover, we wanted to avoid an additional synthetic step. Accordingly, we set out to develop conditions for a one-pot cycloaddition and oxidation.

Our initial goal was to find an oxidant that could oxidize the sulfoxide **1.194** to the sulfone **1.200**. To avoid the additional complication of running the cycloaddition prior to screening each potential oxidant, we instead added various oxidants to a solution of pure **1.194** in dichloromethane (Scheme 1.62). No reaction was detected with aqueous hydrogen peroxide. Addition of mCPBA resulted in a rapid oxidation of **1.194** to a mixture (2:1) of **1.200** and epoxy-sulfone **1.201**. Oxone failed to react with **1.194** until acetone was added to the reaction mixture, whereupon it gave a mixture (25:1) of **1.200** and over oxidized side product **1.201** in 95% yield. The formation of **1.201** might arise from the generation of dimethyldioxirane from acetone and Oxone.

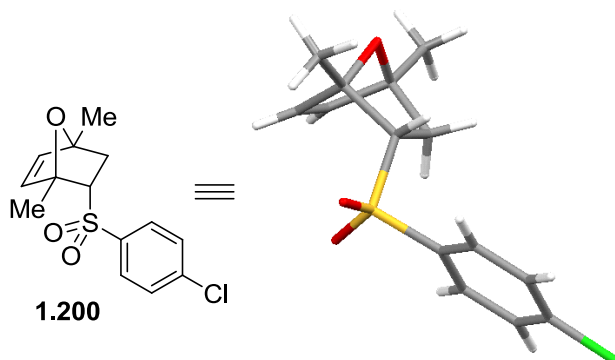
To better simulate the quench with NaHCO_3 during the one pot cycloaddition/oxidation sequence, we added aqueous NaHCO_3 to a solution of pure **1.194** in dichloromethane prior to the addition of the Oxone and acetone. We found a much poorer ratio (2:1) of sulfone **1.200** and over-oxidized product **1.201**. This may be due to increased formation of DMDO, promoted by the NaHCO_3 .⁷⁹ By lowering the temperature to 0 °C the over oxidation could be better controlled, giving a mixture (13:1) of **1.200** and **1.201** in 90% yield. The structure of the main product **1.200** was confirmed by X-ray crystallography (Figure 1.14). These conditions set the stage to attempt the one-pot reaction.

Scheme 1.62: Model study for determining optimal oxidative workup conditions



$[O] =$	Result:	Ratio (1.200:1.201):
•H ₂ O ₂ (30% aq.)/CH ₂ Cl ₂	No Rxn	-
•mCPBA, -78-rt	>90%	2:1
•Oxone (H ₂ O/MeOH)	No Rxn	-
• Oxone (H₂O/acetone)	95%	25:1
•Oxone (H ₂ O/NaHCO ₃ /acetone)	>95%	2:1
• Oxone (H₂O/NaHCO₃/acetone), 0 °C	90%	13:1

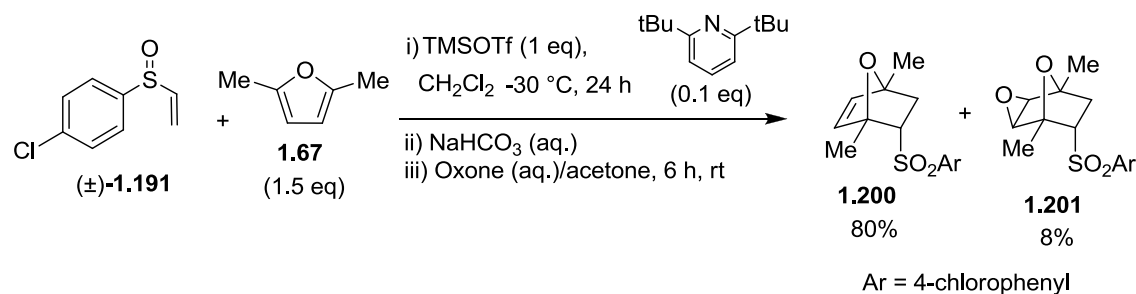
Figure 1.14: X-ray crystal structure of oxidized cycloadduct **1.200**



A one-pot cycloaddition, quench, and oxidation was performed with vinyl sulfoxide **1.191** and dimethylfuran **1.67** the optimized cycloaddition conditions. After quenching the reaction with aqueous NaHCO₃, Oxone and acetone were added, and the

mixture was stirred for 6 h at room temperature; the sulfone **1.200** was thus isolated in 80% yield along with epoxide **1.201** in 8% yield (Scheme 1.63).

Scheme 1.63: One-pot cycloaddition and oxidation procedure



The one-pot oxidative workup procedure was then modified to use triethylamine instead of NaHCO₃ as the quenching base; the use of triethylamine improved the yield and minimized the amount of over oxidized product **1.201**. We now sought to conduct this new one-pot sequence with each furan, and the results are summarized in Table 1.7. Although the yield of the cycloadducts **1.200** and **1.202** dropped slightly to 81 and 88%. The stereoselectivity of the reaction remained the same in all examples.

Table 1.7: Optimized cycloaddition for all substrates using oxidative workup protocol

Ar = 4-chlorophenyl

1.200, 1.202, or 1.203

furan	product	L.A. eq.	furan eq.	temp. (°C)	yield (%)	endo:exo ^a	endo ee (%) ^b
	1.203	1	5	0	98	1.8:1	88
	1.202	0.75	2	-30	81	25:1	99
	1.200	0.50	2	-30	88	25:1	98

^a determined by integration of the characteristic α -sulfonyl protons of the ¹HNMR spectrum. ^b determined by chiral HPLC.

1.203 **1.202** **1.200**

1.4.2. Development of the Ring-Opening Cross Metathesis (ROCM)

With an established method for the asymmetric synthesis of substituted oxabicycles, we turned our attention toward developing techniques for elaborating such systems into tetrahydrofurans such as **1.1**. Specifically, we were interested in routes to open oxabicyclic systems such as **1.194** or **1.200** by either cleavage of the olefin, thereby generating a tetrahydrofuran. One method of interest was by ring-opening cross metathesis, which had been applied to on similar substrates (Scheme 1.14).⁴¹

Initial explorations into the ROCM were performed using oxabicyclic sulfoxide **1.181**. Our screening began using conditions comparable to those reported by Rainier for a similar oxabicyclic system, wherein ethyl vinyl ether was used as a metathesis cross-partner.⁴¹ A solution of cycloadduct **1.181** and ethyl vinyl ether was exposed to a variety of common metathesis catalysis (Scheme 1.64), including Grubbs 1st generation catalyst **1.204**, Grubbs 2nd generation catalyst **1.205**, or Hoveyda-Grubbs 2nd generation catalyst **1.206** (Figure 1.15). However, all catalysis failed to give any of the desired tetrahydrofuran **1.207**. The regioselectivity shown in Scheme 1.64 reflects that of the example by Rainier (Scheme 1.14).

Scheme 1.64: Early attempts at ring-opening cross metathesis

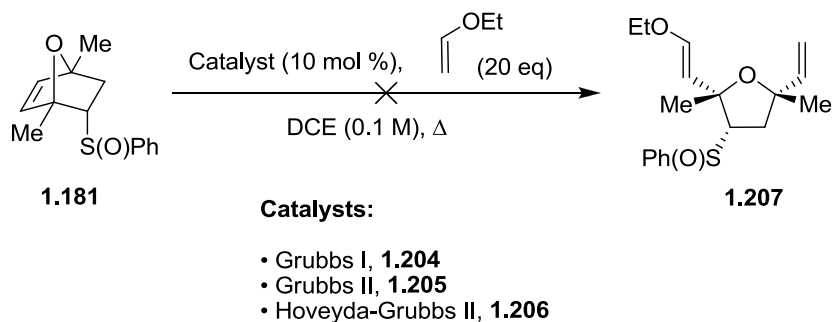
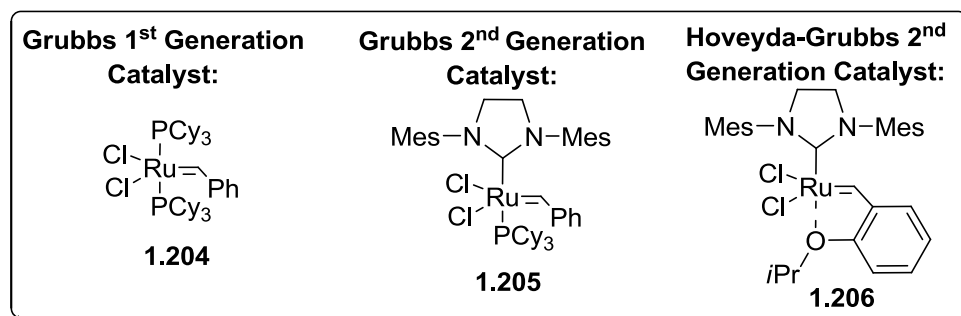
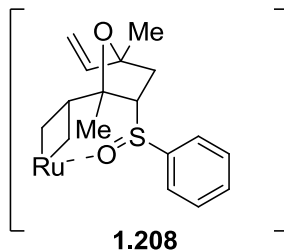


Figure 1.15: Metathesis catalysts

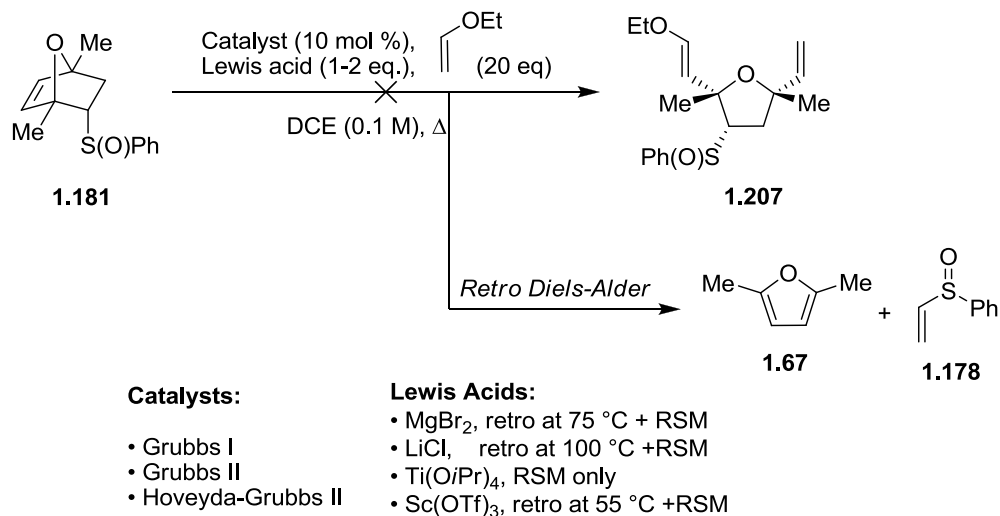


Sulfoxides are known to complex with ruthenium catalysts, so we hypothesized that the Lewis-basic oxygen atom of the sulfoxide might be forming a chelate such as **1.208** thereby halting the catalysis (Figure 1.16).⁸⁰ In an effort to break up this putative interaction, we screened several Lewis acids, but, MgBr_2 , LiCl , and $\text{Sc}(\text{OTf})_3$ all failed to give any trace of ring-opened tetrahydrofuran **1.207**; upon heating these reaction the retro [4+2] cycloaddition ensued (Scheme 1.65). $\text{Ti}(\text{OiPr})_4$ was the only Lewis acid that did not promote the retro-cycloaddition; but, it also failed to induce the ROCM.

Figure 1.16: Possible catalyst chelation with the sulfoxide oxygen

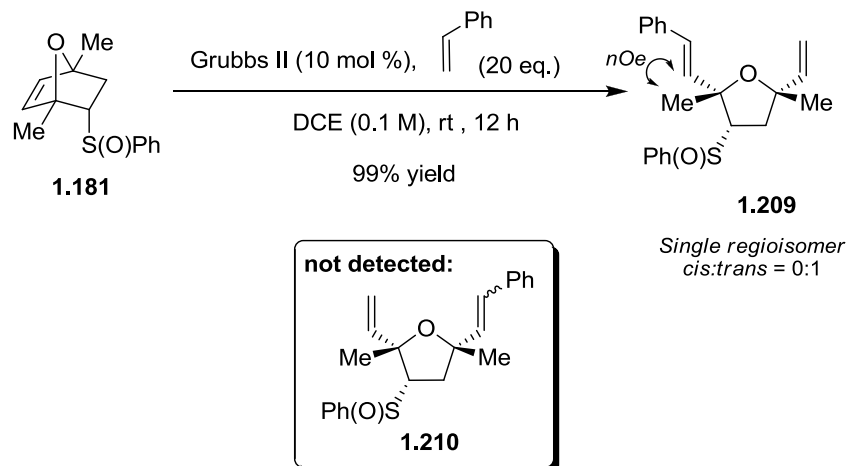


Scheme 1.65: Attempts at ROCM with Lewis acid additives



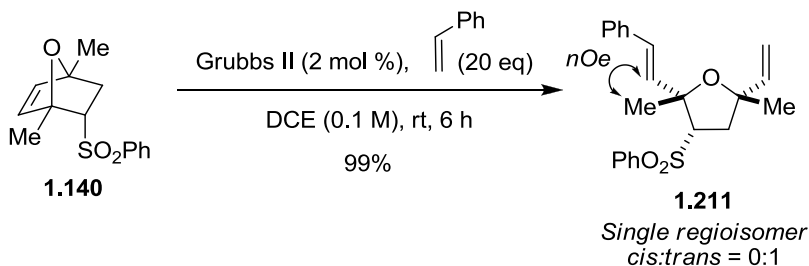
When a similar reaction was performed with **1.181** and styrene the tetrahydrofuran **1.209** was isolated in 99% yield and the ring opened material was isolated in 99% yield, as a single regio- and diastereoisomer (Scheme 1.66). No **1.210** was detected. The regiochemical structural assignment was based on the nOe coupling between the vinylic protons of the styrene moiety and the tertiary methyl group. The *trans* configuration was assigned based upon the coupling constants of the vinylic protons ($J = 15.9$ Hz). Catalyst loading lower than 10 mol % resulted in exceptionally long reaction times and low yields.

Scheme 1.66: First successful ring-opening cross metathesis using styrene



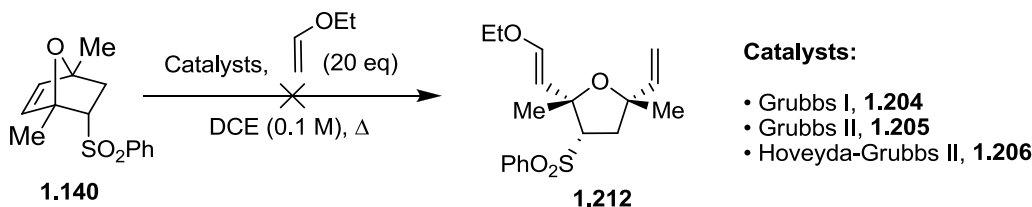
The ROCM of styrene with sulfoxide **1.181** required a high catalyst loading, so, we queried whether the ROCM with the less Lewis basic sulfone **1.140** might require less catalyst. We found that sulfone **1.140** reacted with styrene to give tetrahydrofuran **1.211** as a single regio- and stereoisomer in 99% yield and required only 2 mol % catalyst loading (Scheme 1.67). The structural assignments were made on the basis of the *n*Oe interaction between the vinylic protons and the tertiary methyl groups. The *trans* configuration was assigned based on the coupling constants ($J = 15.8$ Hz) of the vinylic protons.

Scheme 1.67: Improved results using the sulfone auxiliary



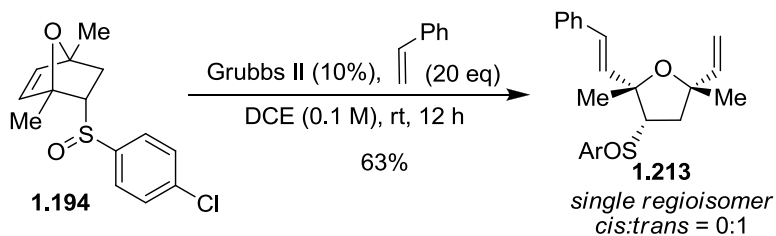
However, **1.140** failed to react with ethyl vinyl ether in the presence of any of the catalysts **1.204-1.206** (Scheme 1.68). This lack of reactivity was surprising, considering how well this olefin cross-partner performed in similar literature reports.⁴¹

Scheme 1.68: No reaction with ethyl vinyl ether cross-partner



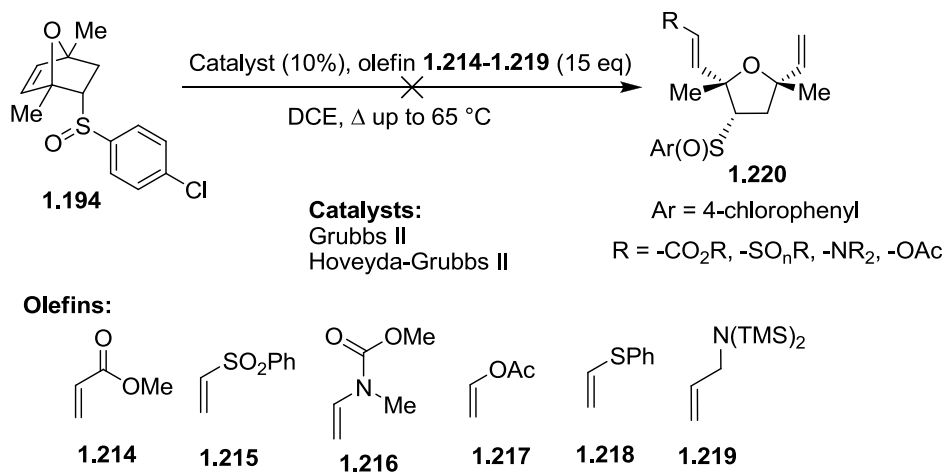
Since the cycloaddition of the *p*-chlorophenyl substituted vinyl sulfoxide **1.191** with furans were higher yielding than those with **1.178**, we examined the ROCM reaction of cycloadduct **1.194**. The ring opening cross-metathesis of **1.194** delivered **1.213** as a single isomer, but the yield was only 63% (Scheme 1.69). The reason for this decrease in yield is unknown, although it could be due to the more electron deficient nature of oxabicyclic **1.194** as compared to **1.140**.

Scheme 1.69: Cross metathesis of cycloadduct **1.194**



The reactions of a number of electronically diverse cross partners **1.214-1.219** were screened under similar conditions, but, all of them failed to give any trace of the desired product **1.220** (Scheme 1.70).

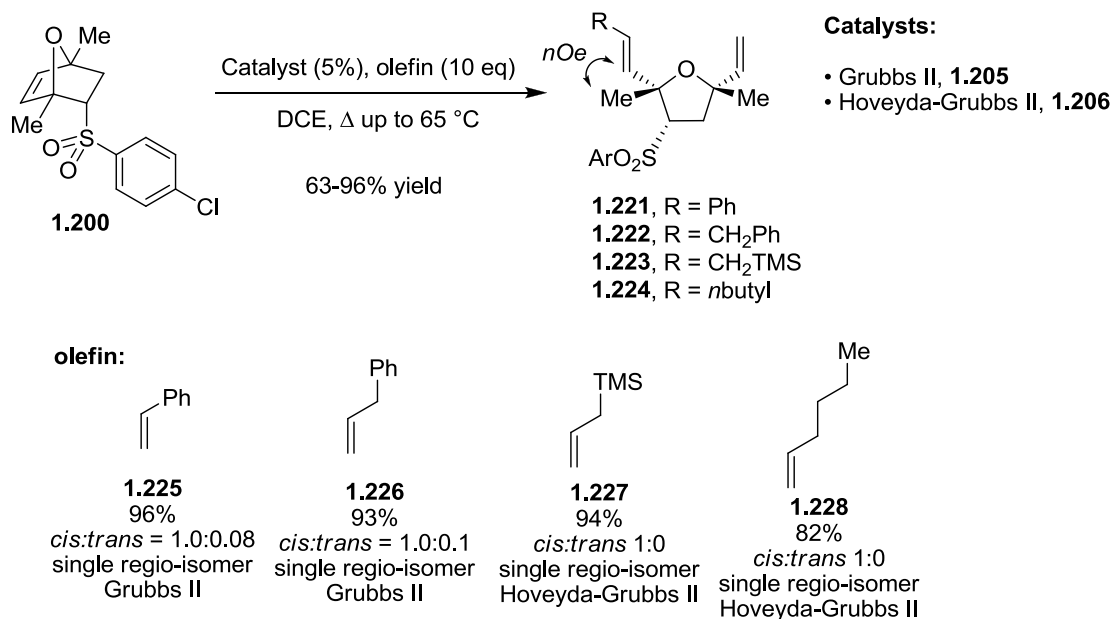
Scheme 1.70: Failed cross metathesis olefins with substrate **1.194**



Again suspecting that the Lewis basic oxygen atom of the sulfoxide might be interfering with the cross metathesis reaction, we explored the ROCM reaction of the

sulfone **1.200** in the presence of Grubbs II **1.205** or Hoveyda-Grubbs II **1.206** catalysts and a with variety of cross-partners (Scheme 1.71).

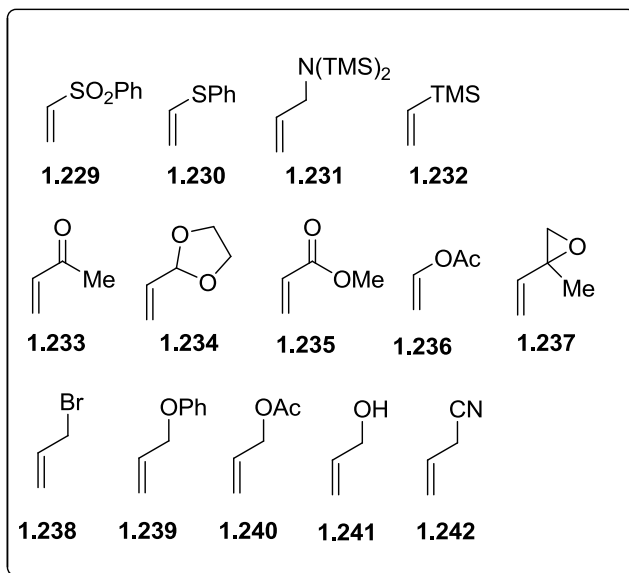
Scheme 1.71: Successful ring opening of cycloadduct **1.200** with various cross partners



We screened a wide range of cross-partners, with varied results. Some cross-partners such as **1.225-1.228** were excellent substrates, giving yields of **1.221-1.224** between 82% and 96%, but other olefins such as **1.229-1.242** (table 1.8) were completely unreactive. Examination of the structures of successful cross-partners reveals that only non-polar cross-partners work well in this ROCM. It is unclear why this is the case. Tetrahydrofurans **1.221-1.224** were isolated as a single regio- and stereoisomer. The structural assignments were made on the basis of the nOe interaction between the vinylic

protons and the tertiary methyl groups. The *trans* configuration of the alkenes were assigned based on the coupling constants of the vinylic protons.

Table 1.8: Unreactive olefin cross-partners with cycloadduct **1.200**



In an effort to gain some insight into origin of the regioselectivity of the ROCM, *endo*-sulfone **1.200** (Scheme 1.72) and *exo*-isomer **1.243** (Scheme 1.73) were compared. These systems were of interest because the inductive effect from the electron withdrawing sulfones in both systems should be very similar, so a difference in the regioselectivity of these two systems will be primarily a comparison of steric and coordinative effects. *Endo*-sulfone **1.200** was allowed to react with an excess of allyltrimethylsilane in the presence of Hoveyda-Grubbs II (**1.205**), and the product **1.223** was isolated in 94% yield (Scheme 1.72). The structure of tetrahydrofuran **1.223** was

initially assigned by nOe NMR experiments and later confirmed by X-ray crystallography (Figure 1.17).

Scheme 1.72: Cross metathesis of *endo* **1.200** with allyltrimethylsilane

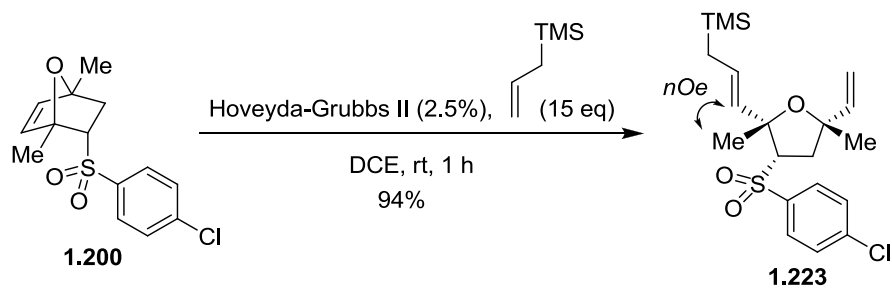
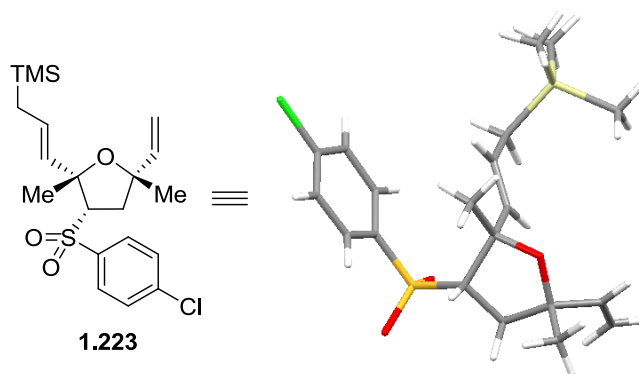


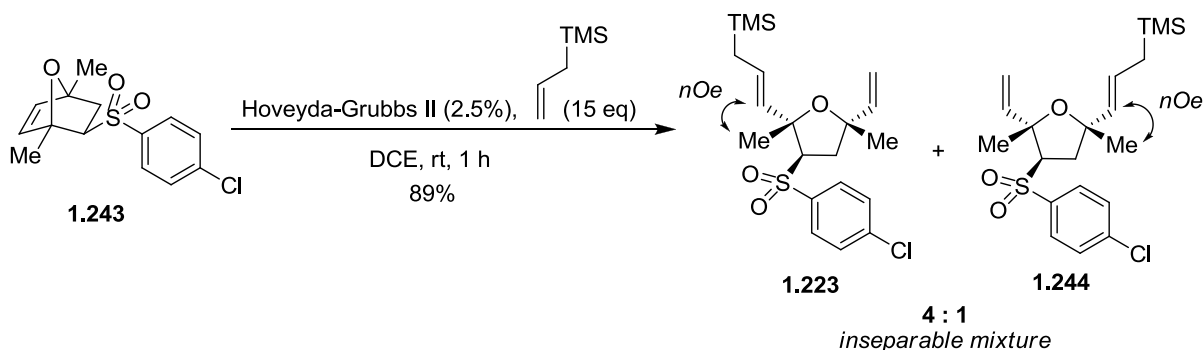
Figure 1.17: X-ray structure of tetrahydrofuran **1.223**



When the *exo*-sulfone **1.243** was allowed to react with allyltrimethylsilane under identical conditions, an inseparable mixture (4:1) of the expected isomer **1.223** and the regioisomer **1.244** was isolated in 89% combined yield (Scheme 1.73). This is

significant, but not total erosion in regioselectivity. While there is a slight difference in reactivity between *endo*-**1.200** and *exo*-**1.243**, they both gave **1.223** as the major product, suggesting that the regioselectivity is based in part due to on the electron withdrawing nature of the sulfone, which may polarize the olefin for a regioselective cross-metathesis. This polarization effect, which is approximately equivalent in both the case of **1.200** and **1.243** is not, however, does not account for the observed difference in regioselectivity.

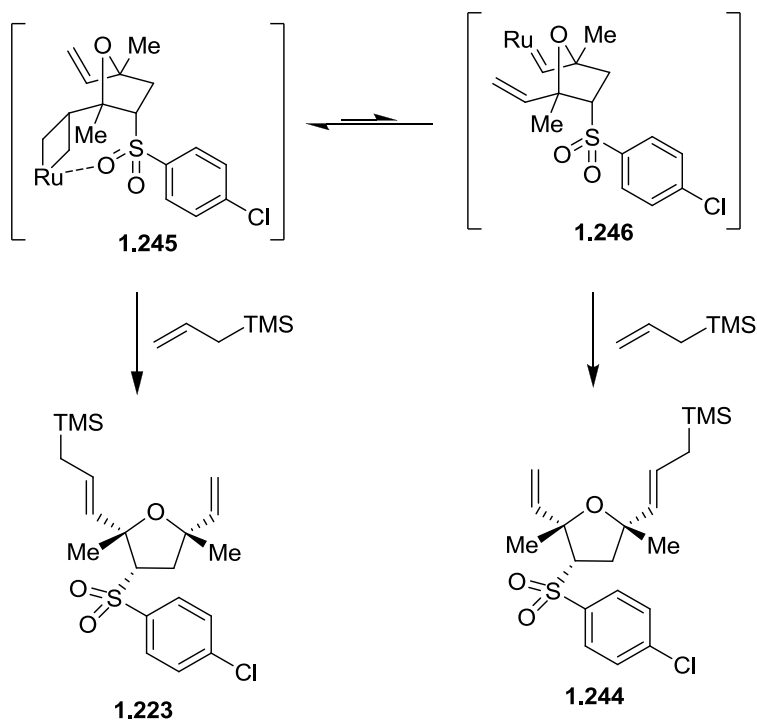
Scheme 1.73: Reaction of *exo*-cycloadduct **1.243** and detection of the other regioisomer



The slight erosion in the regioselectivity in the case of **1.243** may be accounted for in by loss of a coordinative affect that is present only in the *endo* isomer **1.200**. This coordination effect could be manifested through a stabilized intermediate such as **1.245** and intermediate **1.246** (Figure 1.18). When the metathesis catalyst loads onto an oxabicycle such as **1.200**, it can either load to the olefin terminus proximal to the sulfone, generating intermediate **1.245**, or it can load onto the terminus opposite the sulfone leading to intermediate **1.246**. Alkylidene intermediate **1.245** may be stabilized by a coordination of the metal center of the catalyst to the sulfone oxygen atoms, discouraging its interconversion to alkylidene **1.246** and leading to a majority of tetrahydrofuran **1.223**.

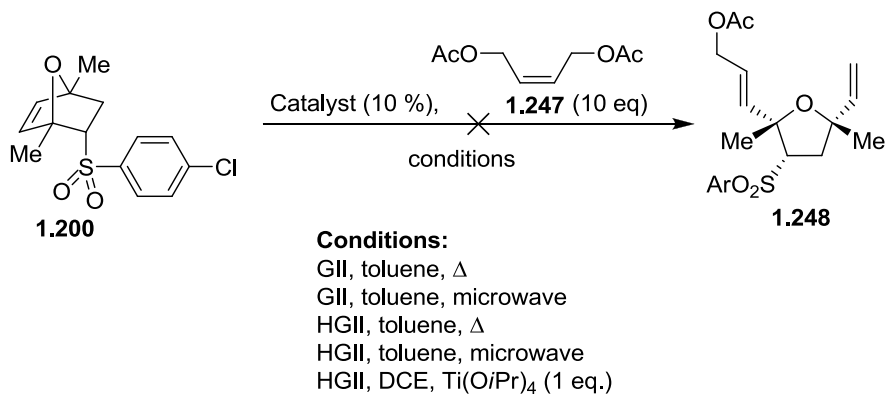
We speculate that the **1.245** is the kinetically and thermodynamically favored alkylidene, and when the intramolecular coordination is not present as in **1.243**, the stabilization effect from the sulfone is lost and the preference of **1.245** over **1.246** is lessened. The structural assignments of tetrahydrofurans **1.223** and **1.244** were made on the basis of the nOe interaction between the vinylic protons and the tertiary methyl groups. The *trans* configurations of **1.223** and **1.244** were assigned based on the coupling constants of ($J = 15.2$ Hz and 15.1 Hz) of the vinylic protons.

Figure 1.18: Possible stabilized intermediate related to the sulfone directing effect



Only unpolarized olefins had been used successfully as reaction partners for the ROCM sequence (Scheme 1.71). Efforts were thus directed to conduct the ring-opening reaction with a more functionalized cross partner. Efforts to use allyl acetate **1.240** as a cross metathesis partner failed (Table 1.8). However, 1,4-cis-butene-diacetate (**1.247**), which is known to be a highly reactive cross-partner due to the relief of the allylic strain upon metathesis, was chosen for the screening.⁸¹ The product of a cross metathesis reaction with 1,4-cis-butene-diacetate (**1.247**) contains a functional handle for further transformations *via* well-precedented allylic alkylation chemistry.^{82,83} However, oxabicycle **1.200** failed to react with 1,4-cis-butene diacetate (**1.247**) under conventional ROCM conditions (Scheme 1.74). The starting material **1.200** unreactive even with microwave heating or in the presence of Ti(OiPr)₄. The only identifiable product was 10 mol % of cinnamyl acetate (**1.249**), which was formed as a side product corresponding to the cross-product of Grubbs II catalyst with 1,4-cis-butene diacetate (**1.247**). The isolation of **1.249** suggests that the allyl acetate alkylidene species **1.250** is being formed, but it is apparently unreactive with **1.200** under these conditions (Figure 1.19).

Scheme 1.74: Absence of reactivity with 1,4-cis-butene diacetate cross-partner



All reactions gave recovered starting material. This side product isolated in equimolar amounts to the loading of GII:

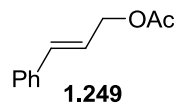
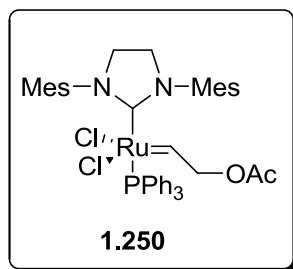


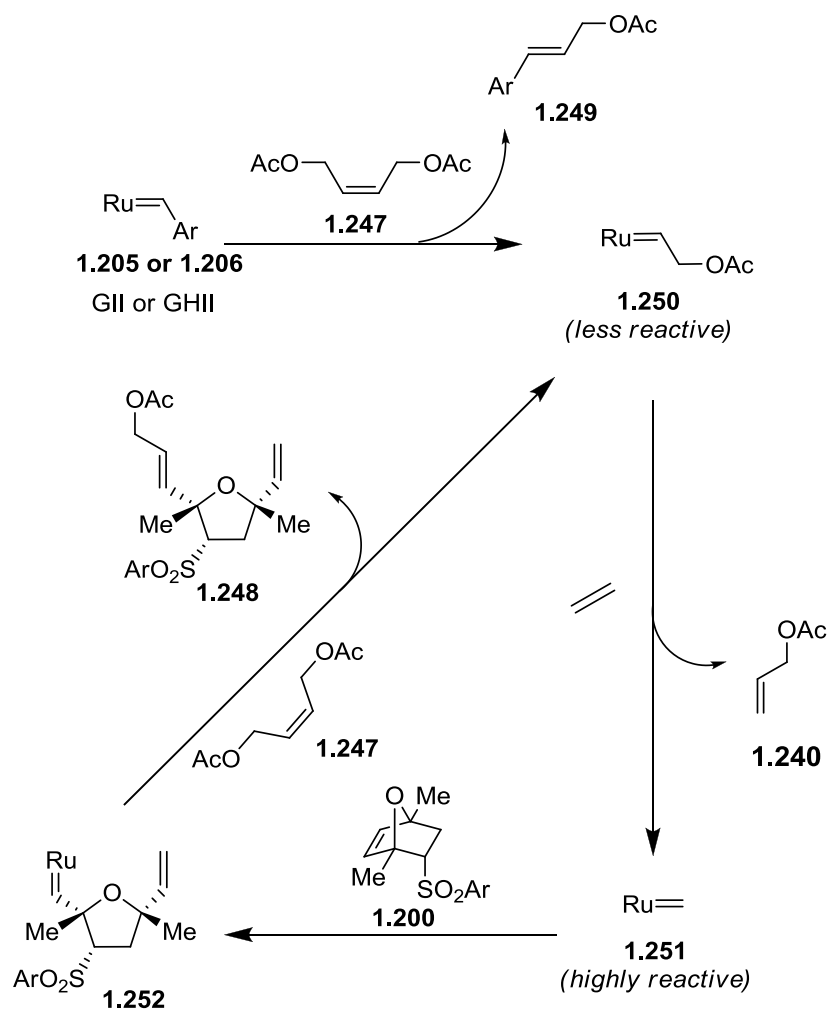
Figure 1.19: Likely allyl acetate intermediate alkylidene species



On the suspicion that the alkylidene species **1.250** was unreactive with oxabicyclic **1.200**, we envisioned that we might be able to encourage the ring-opening of **1.200** by exchanging the alkylidene of **1.250** with a more reactive alkylidene such as a ruthenium-methylidene such as **1.251** (Scheme 1.75). The envisioned catalytic cycle, as

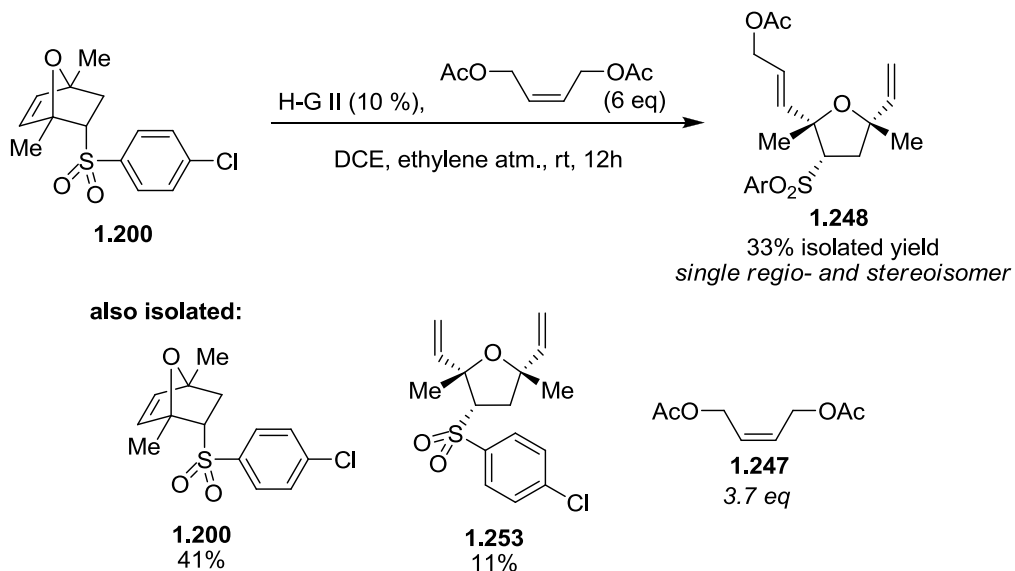
outlined in Scheme 1.75, would begin with either Grubbs II or Hoveyda Grubbs II catalyst reacting with 1,4-cis-butene diacetate (**1.247**) to give the unreactive alkylidene **1.250** along with cross product **1.249**. Alkylidene **1.250** could then react with ethylene to form the highly reactive methyldiene **1.251**, which could allow for the loading of the ruthenium catalyst onto oxabicyclo **1.200**. Subsequent ring-opening to species **1.252** followed by cross-metathesis with the desired cross-partner would give the product **1.248**.

Scheme 1.75: Proposed pathway to overcome unreactive alkylidene intermediates



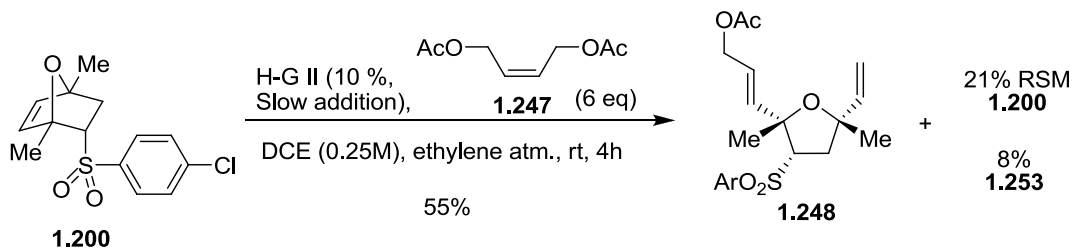
Gratifyingly, when the ROCM with 1,4-cis-butene-diacetate (**1.247**) was conducted under an ethylene atmosphere, the desired product **1.248** was isolated in 33% yield as a single regio- and stereoisomer, along with 41% of the unreacted starting material **1.200**, 11% of the ethylene cross product **1.253** and unreacted 1,4-cis-butene diacetate (**1.247**) (Scheme 1.76).

Scheme 1.76: Results of ring-opening cross metathesis under ethylene atmosphere



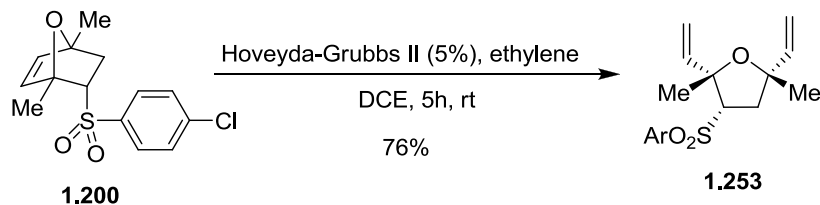
Varying the catalyst, reaction temperature, solvent, equivalents of **1.247**, rate of addition, and order of addition eventually lead to the optimal conditions that yielded 55% of **1.248** along with 21% of unreacted starting material **1.200** and 8% of ethylene cross product **1.253** (Scheme 1.77). If more 1,4-cis-butene diacetate (**1.247**) was added, the reaction became sluggish; likewise, if less than six equivalents of **1.247** was used, the reaction slowed down. Solvent changes had a negligible effect on the reaction. Slow addition of the catalyst over two hours improved the yield significantly.

Scheme 1.77: Optimized cross-metathesis conditions under ethylene atmosphere

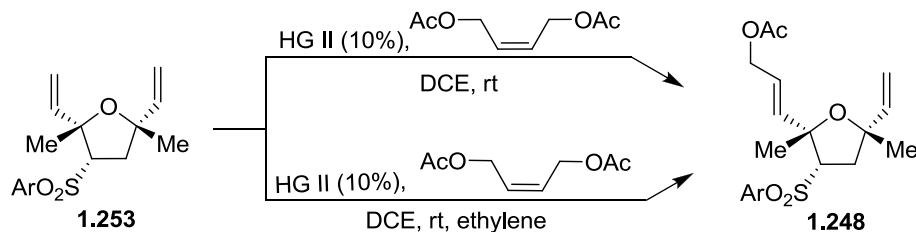


If ethylene is aiding in the ring-opening process to access an intermediate such as **1.252**, a question arises as to whether that intermediate directly reacts with 1,4-cis-butene diacetate (**1.247**) or whether the system first reacts with ethylene to give **1.253**, which then reacts with the olefin partner **1.247**. In order to probe this question, the ethylene ROCM product **1.253** was prepared in 76% yield (Scheme 1.78). When **1.253** was exposed to standard cross metathesis conditions with 1,4-cis-butene diacetate (**1.247**) in the presence and absence of ethylene (Scheme 1.79), no **1.248** was formed. The results of this experiment support a hypothesis that the carbene **1.252** reacts directly with 1,4-cis-butene diacetate (**1.247**), but allyl acetate **1.240** does not.

Scheme 1.78: Cross metathesis of cycloadduct **1.200** using ethylene

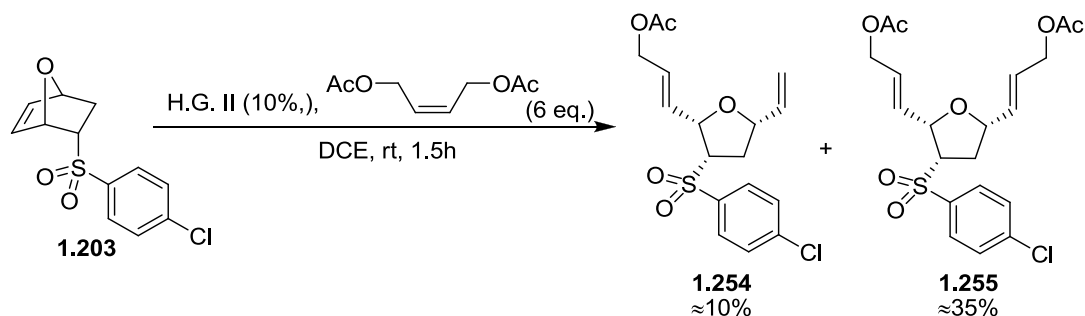


Scheme 1.79: Probing the reaction pathway



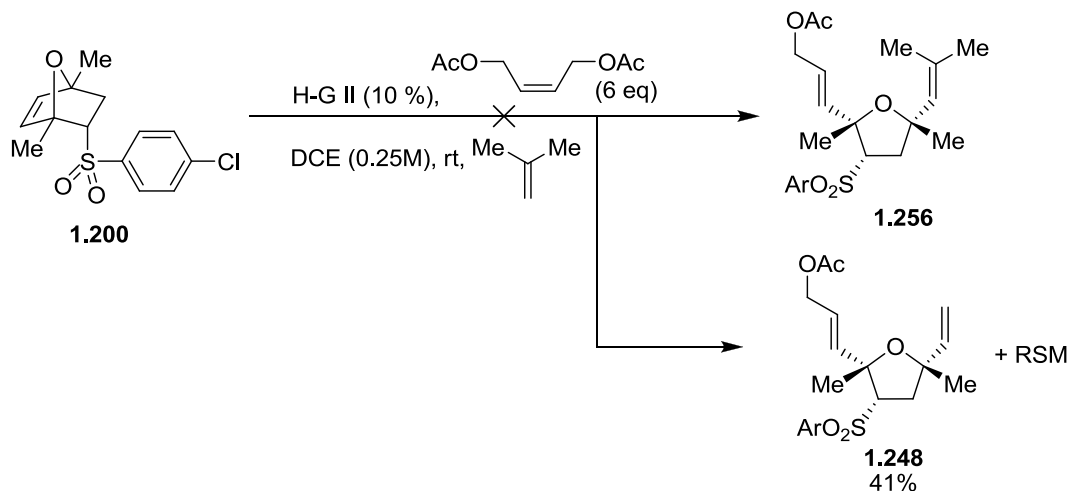
To further probe the mechanism of the ROCM of **1.200** with 1,4-cis-butene diacetate (**1.247**), the unsubstituted oxabicyclic **1.203** was prepared and exposed to Hoveyda Grubbs II catalyst and 1,4-cis-butene diacetate (**1.247**) under an argon atmosphere. This less-substituted bicyclic substrate was extremely reactive under these conditions, giving a mixture of several products, including approximately 10% of **1.254** and 35% of the double cross-product **1.255** (Scheme 190). The fact that this system was much more reactive than **1.200** and did not require an ethylene atmosphere suggests that the bridgehead methyl groups of **1.200** impart a steric penalty that a less reactive alkylidene such as **1.250** is unable to load onto the oxabicyclic. When a highly reactive alkylidene such as **1.251** is present, it has sufficient reactivity to load onto the sterically congested oxabicyclic **1.200**, thus leading to ring-opened intermediate **1.252**. Intermediate **1.252** can then react with 1,4-cis-butene diacetate (**1.247**), which may be present in solution in greater concentration than ethylene gas.

Scheme 1.80: Further probing of the cross metathesis.



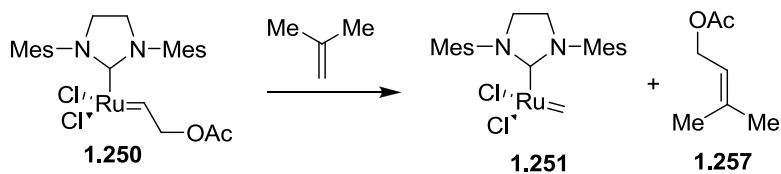
High temperatures are detrimental to ring-opening cross metatheses conducted under an ethylene atmosphere, so we hypothesized that the methyldiene alkylidene **1.251** was decomposing at higher temperatures. We hypothesized that we might improve the yield and the catalytic turnover of this reaction if we substituted ethylene with a substituted olefin such as 2-methylpropene. The ruthenium alkylidene of this olefin might be more stable to the reaction conditions than the methyldiene **1.251**. Whether **1.256** or **1.257** was formed would be dependent upon the regioselectivity of the alkylidene formation with 2-methylpropene (Scheme 1.81). Indeed, when **1.200** was exposed to Hoveyda-Grubbs II catalyst and cis-butene diacetate (**1.247**) under an atmosphere of 2-methyl propene gas, we did not see any formation of **1.256**, and we isolated **1.248** in 41% yield.

Scheme 1.81: Probing the mechanism of the cross metathesis using methylpropene gas



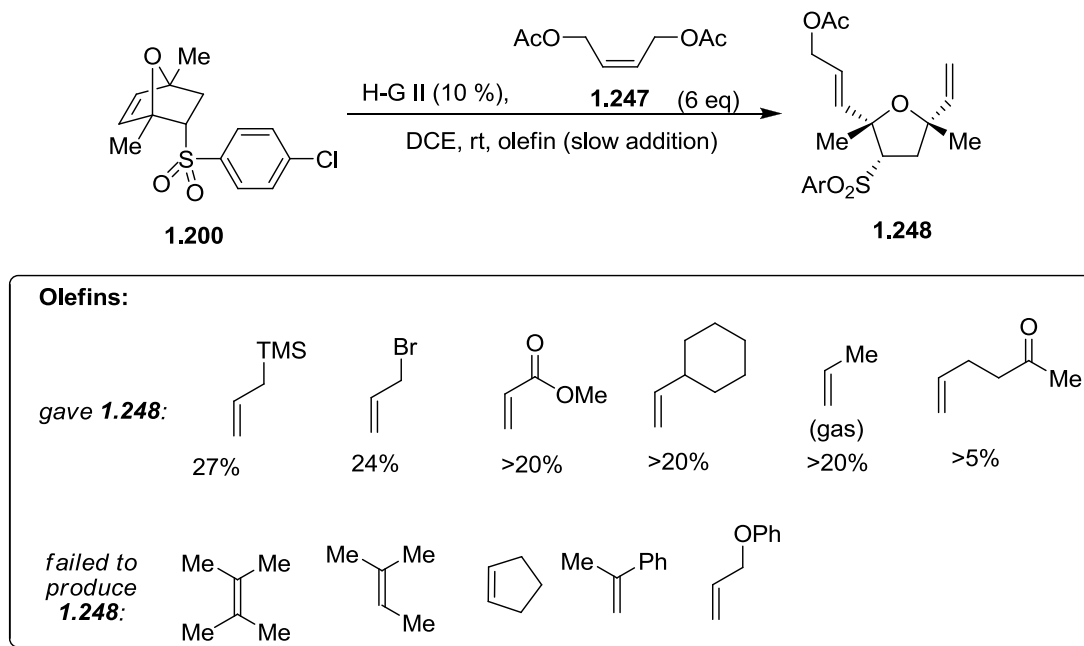
Presumably, 2-methylpropene reacted with alkylidene **1.250**, which would have been generated by the cross metathesis of Hoveyda-Grubbs catalysts with 1,4-cis-butene diacetate (**1.247**). This would have given the reactive methyldiene species **1.251** along with allyl acetate cross product **1.257** (Scheme 1.82), though we did not specifically observe the formation of either. Methyldiene **1.251** may also arise from Hoveyda-Grubbs II (**1.205**) by a similar pathway.

Scheme 1.82: Proposed mechanistic pathway to generate product **1.257**



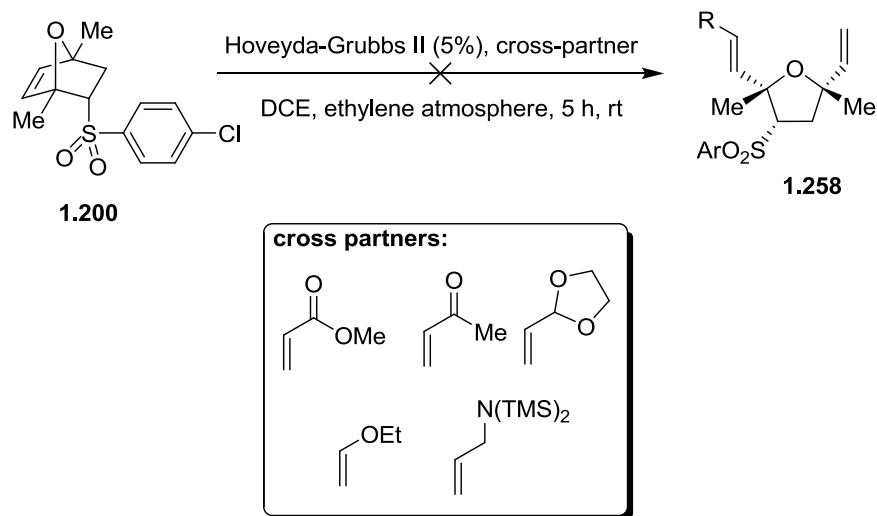
We queried whether we might use other olefins in place of ethylene in order to improve the yield and catalytic turnover of the ROCM of **1.200** and **1.247** to give **1.248**. To test this hypothesis, we performed a number of experiments wherein we added different olefins to the ring-opening cross metathesis reaction of **1.200** in place of ethylene. We added the olefins drop wise over a few hours as to avoid overloading the catalyst with multiple cross-partners and to facilitate a slow but constant generation of the presumed active species **1.251** (Scheme 1.83). While we were pleased to see that we could generate the desired product **1.248** in such a manner, the yields were disappointingly low. When **1.248** was formed, traces of the cross metathesis products with the unintended olefins were detected in all cases in low yield. The most successful reaction was by the dropwise addition of allyltrimethylsilane to the reaction, which gave the desired product in 27% yield.

Scheme 1.83: Addition of various simple olefins in place of ethylene



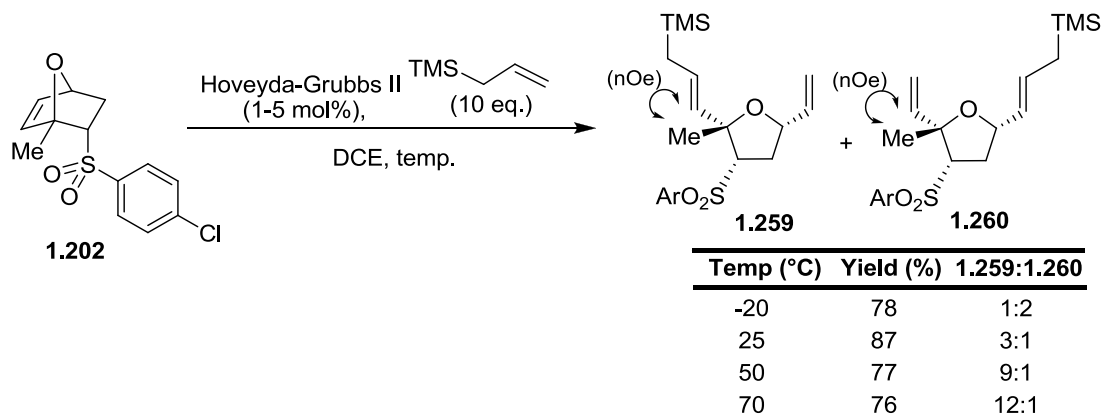
In hopes that we might extend this ethylene atmosphere technique to functionalized cross-partners besides 1,4-cis-butene diacetate (**1.247**), we screened a number of functionalized olefins with oxabicyclo **1.200** under similar conditions (Scheme 1.84). Unfortunately, all of the olefins screened failed to give a detectable amount of the desired products **1.258**. This is perhaps due to the importance of two factors when using functionalized olefins: (1) There must be a pathway to generate alkylidene **1.251** (2) The olefin cross partner must be reactive enough to undergo metathesis with the sterically hindered neopentyl alkylidene **1.252**. Functionalized cross partners without the strain relief advantage of **1.247** may have difficulty reacting with neopentyl alkylidene **1.252**.^{84,85}

Scheme 1.84: Failure of the ethylene atmosphere technique with other cross-partners



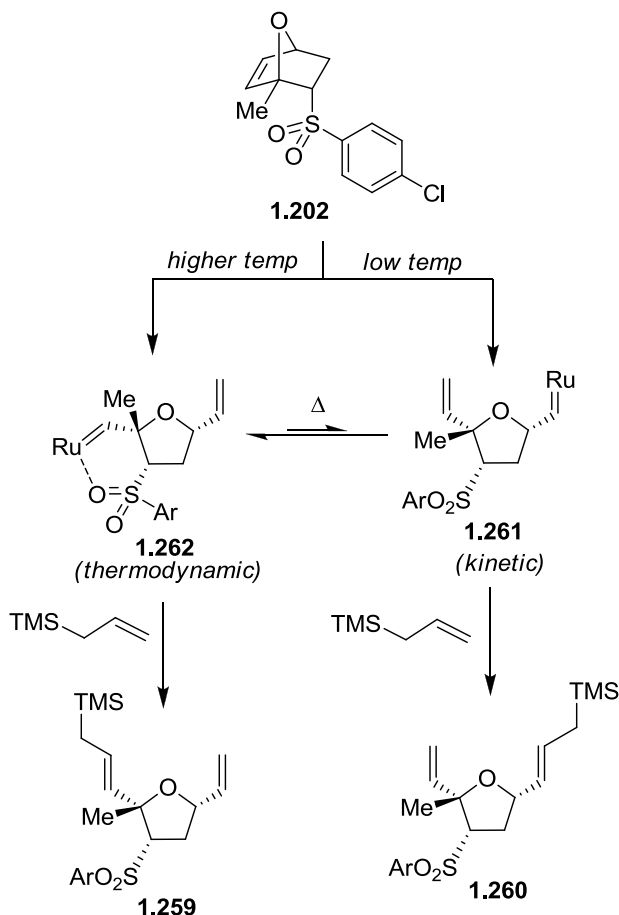
We then examined the ROCM of the mono-substituted oxabicyclo **1.202**. We found that sulfone **1.202** reacted with an excess of allyltrimethylsilane, in the presence of Hoveyda-Grubbs 2nd generation catalyst **1.206**, to give a mixture of regioisomers **1.259** and **1.260** (Scheme 1.85). Interestingly, the course of the reaction was temperature dependent. Namely, when the reaction was performed at low temperature, regioisomer **1.260** was favored over **1.259** in a 1:2 ratio. When the reaction was run at room temperature, we observed a switch in the major product, giving **1.259** and **1.260** in a 3:1 ratio. Performing the reaction at 50 °C led to a 9:1 mixture of **1.259** and **1.260**. Finally, when the reaction temperature was raised to 70 °C, we observed a very selective reaction, favoring **1.259** over **1.260** in a 12:1 ratio in 76% yield. Further increases in the reaction temperature failed to improve this ratio. The main regioisomer was characterized by an nOe signal from the methyl group to the proximal vinylic protons.

Scheme 1.85: ROCM of mono-substituted system



To probe whether the temperature dependence of the ring opening cross-metathesis of **1.202** with allyltrimethylsilane was due to an equilibration between **1.259** and **1.260**, we resubjected purified **1.259** and **1.260** to the reaction conditions; however, no equilibration was observed. We speculate that this that the temperature dependence may be based on a kinetically formed alkylidene **1.261**, which is formed initially at the less sterically hindered carbon (Scheme 1.86). This kinetic preference is unique to the mono-substituted oxabicyclic **1.202**, and is not present with alkylidene **1.245**. At higher temperatures **1.261** can equilibrate to alkylidene **1.262**, which is a more thermodynamically stable due to a stabilizing effect with the proximal sulfone. Thus, at low temperatures alkylidene **1.261** reacts with allyltrimethylsilane to give **1.260** and at high temperatures the predominant alkylidene **1.262** leads to **1.259**.

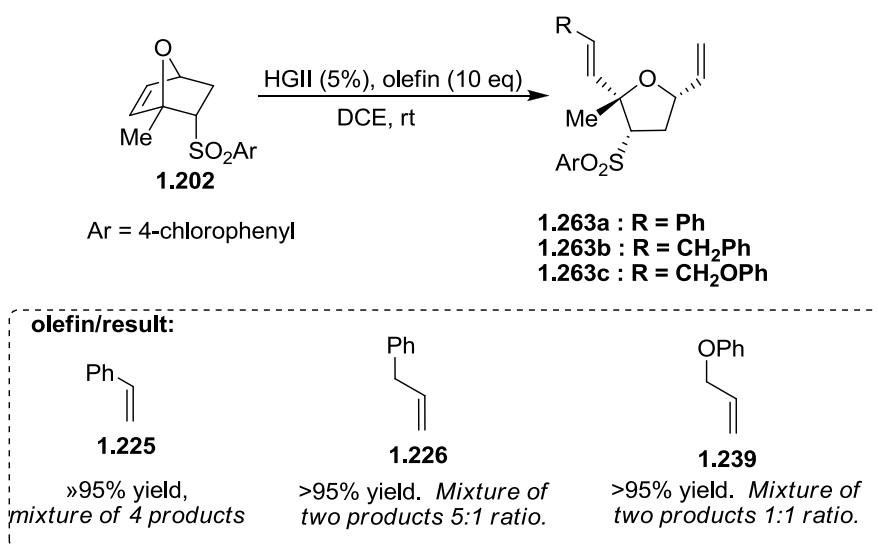
Scheme 1.86: Possible temperature dependent alkylidene formation



Several other olefins were screened in order to expand the scope of ROCM reaction of **1.202** (Scheme 1.87) to give **1.263a-c**, but it quickly became apparent that each case would be unique in terms of the regioselectivity and yield. For example, the reaction of **1.202** with styrene (**1.225**) gave a complex mixture of what appears to be four different products by examination of the ^1H NMR spectrum of the crude mixture in excellent yield. While variations in the temperature altered the ratio of these four products, no temperature was found that favored a single product in a synthetically useful ratio. Similarly, use of allylbenzene (**1.226**) as the olefin led to a mixture (5:1) of two

inseparable products in high yield. These products were never characterized, so it was not possible to make regiochemical assignments. Unfortunately, all attempts to improve this ratio by changing the temperature were unsuccessful. Reaction of allyl phenylether (**1.239**) with **1.202** gave a mixture of two products in 1:1 ratio in >95% yield.

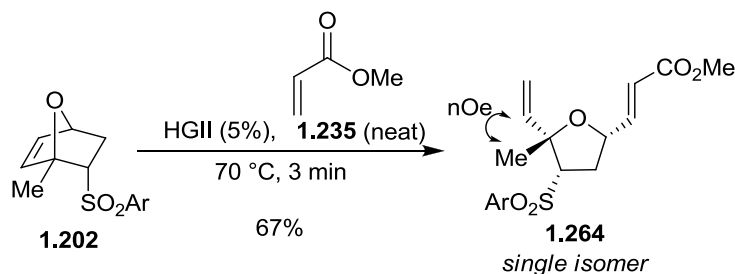
Scheme 1.87: Screening of various metathesis cross-partners



The ROCM of **1.202** with methylacrylate (**1.235**) in the presence of Hoveyda-Grubbs II gave **1.264** as a single regioisomer (Scheme 1.88). The structural assignment of tetrahydrofuran **1.264** was made on the basis of the nOe interaction between the vinylic protons and the tertiary methyl group. The *trans* configurations were assigned based on the coupling constants ($J = 15.7$ Hz) of the vinylic protons. The primary factors affecting the yield of **1.264** were reaction temperature and catalyst loading. Increasing the temperature to 70 °C improved the yield to 41% whereas further increases in

temperature had no effect. Use of 5 mol% catalyst instead of 1% further improved the yield of **1.264** to 67%. Surprisingly, the reaction of **1.202** with **1.268** gave solely the opposite regioisomer as had been seen in previous examples using **1.200**. The reasons behind this are unclear, but this might be because the alkylidene generated from **1.235** is electron deficient, and thus may prefer to open the ring at the opposite terminus of the olefin as with more electron rich olefins.

Scheme 1.88: Optimized conditions for the ROCM with methylacrylate.



It was clear that mono-substituted cycloadduct **1.202** was a more challenging substrate for ROCM, due to a propensity for the formation of both regioisomers. However, after an extensive screening of olefin cross partners, we eventually found several olefins that did react with monosubstituted oxabicyclo **1.202** in a highly selective manner (Table 1.9). The regioisomers were characterized by the characteristic nOe interactions between the quaternary methyl group and proximal vinyl proton (see supporting information).

Table 1.9: Summary of successful ring-opening cross metathesis examples for **1.202**

$\text{1.202} \xrightarrow[\text{DCE, temp.}]{\text{H.G.II, olefin (10 eq.)}}$
 $\text{1.267} + \text{1.268}$

 $\text{Ar} = 4\text{-chlorophenyl}$

olefin ^a	cat. loading (mol %)	temp. (°C)	yield (%)	1.267:1.268	major product
	1	70	76	12:1	1.259
	5	70	67 ^a	0:1	1.264
	1	84	59	1:0	1.265
	2.5	25	99	-	1.266

^a Reaction was run in neat methyl acrylate in a sealed tube; lower yields were obtained upon dilution with solvent.

A summary of the successful ROCM reactions with disubstituted cycloadduct **1.200** is shown in Table 1.10. The results from tables 1.9 and 1.10 constitute the successful development of a ROCM to access a precursor to our final target THFs **1.1**.

Table 1.10: Summary of successful ring-opening cross metathesis examples for **1.200**

<p> <chem>CC1(C)C(=C)C(S(=O)(=O)Ar)C1=O</chem> $\xrightarrow[\text{DCE, temp.}]{\text{H.G.II, olefin (6-10 eq.)}}$ <chem>CC1(C)C(=C)C(S(=O)(=O)Ar)C1=O</chem> </p> <p> 1.202 Ar = 4-chlorophenyl 1.269 </p>				
olefin	cat. loading (mol %)	temp. (°C)	yield (%)	product
<chem>CC(C)=C[Si](C)(C)C</chem>	2.5	25	94	1.223
<chem>C=CC1=CC=CC=C1</chem>	5	25	93	1.221
<chem>C=CC1=CC=CC=C1</chem>	5	0	89	1.222
<chem>CC(=C)COC(=O)C</chem>	10	25	55 ^a	1.248
<chem>C=CC1=CC=CC=C1</chem>	2.5	25	82	1.224
<chem>C=CC1=CC=CC=C1</chem>	5	25	78	1.253

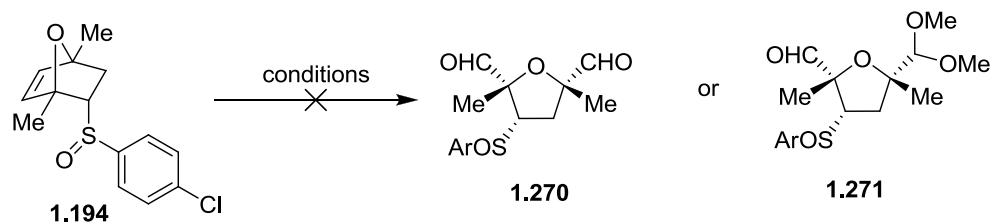
^a Reaction only proceeds under an atmosphere of ethylene.

1.4.3. Development of the oxidative ring-opening

As a complement to the ROCM, we examined the oxidative ring-opening of **1.194** as an option that would allow access to other functionalized tetrahydrofurans from a single oxabicycle. Specifically, an oxidative cleavage of **1.194** would allow access to aldehydes, carboxylic acids, and esters, none of which are directly accessible *via* ROCM.⁸⁶ The oxidative cleavage of similar bicyclic systems has been reported using ozone or Pb(OAc)₄ (Schemes 1.11-1.13).^{32,36}

We sought to develop conditions to prepare functionalized tetrahydrofurans, represented by **1.270** and **1.271** (Scheme 1.89) and a number of ozonolysis conditions were screened with oxabicyclic sulfoxide **1.194**.⁸⁶ Exposure of **1.194** to ozone at low-temperature followed by reductive workup with dimethylsulfide in dichloromethane gave no trace of desired bis-aldehyde **1.270**. In an attempt to access acetal **1.271** cycloadduct **1.270** was allowed to react with ozone and the intermediate was treated with toluenesulfonic acid and then by sodium carbonate and dimethylsulfide. No trace of product **1.273** was ever detected, and only intractable mixtures of unidentified products were obtained.

Scheme 1.89: Failed attempts at oxidative ring-opening

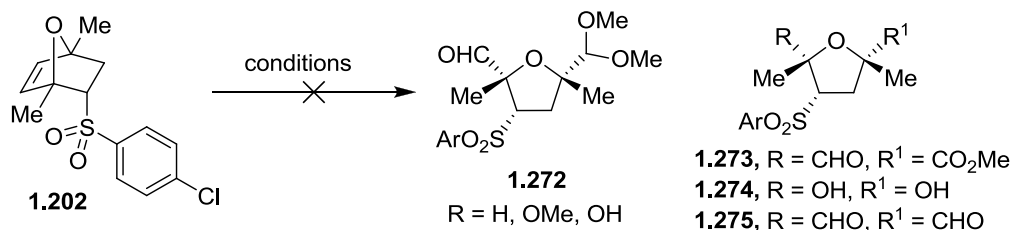


Conditions:

- i. O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ -78°C ; ii. DMS
- i. O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (5:1), -78°C ; ii. *p*-TsOH, rt;
iii. NaHCO_3 ; iv. DMS

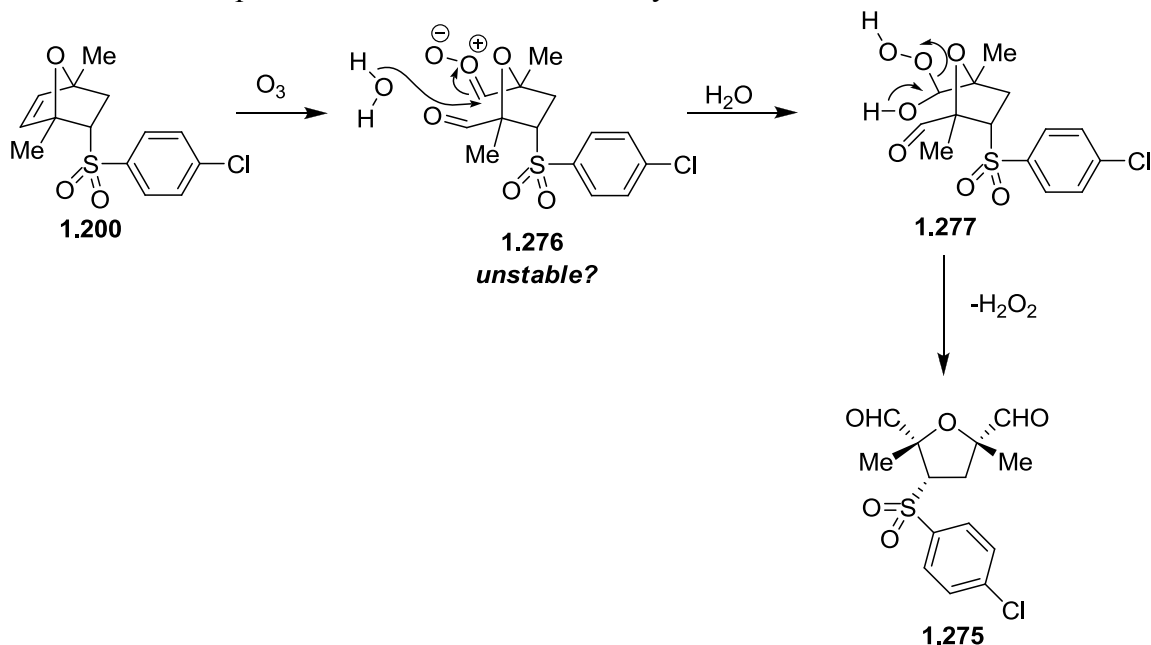
Since the sulfoxide moiety can be oxidized with ozone, we screened a number of common oxidative procedures in an attempt to synthesize compounds **1.272-1.275** from **1.200** (Scheme 1.90). Several ozonolysis conditions were modeled after the procedures published by Schreiber.⁸⁶ In an attempt to prepare acetal **1.272**, cycloadduct **1.200** was subjected to ozone then worked up with toluenesulfonic acid followed by sodium carbonate and dimethylsulfide; however, no trace of the desired acetal was detected. Attempts to access ester **1.273** or diol **1.274** by exposure to ozone in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ and workup using either acetic anhydride/triethylamine or sodium borohydride both failed to generate any of the desired products. We also attempted to cleave the olefin of **1.202** using the Johnson-Lemieux conditions, but exposure of **1.200** to osmium tetroxide and sodium periodate failed to give the desired dialdehyde **1.275**.⁸⁷

Scheme 1.90: Failed attempts to oxidize sulfone substituted cycloadduct **1.200**

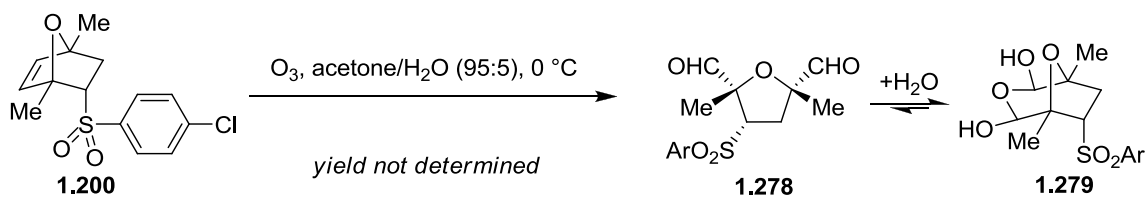


The difficulties with the ozonolysis of **1.200** suggested that some intermediate might be unstable and decompose under the reaction conditions. We were encouraged by a recently published procedure for the direct conversion of alkenes to aldehydes by performing the ozonolysis in wet acetone.⁸⁸ The key feature of this technique was the presence of dissolved water, which intercepted the reactive carbonyl oxide intermediates to produce the dialdehyde. Based on the mechanism proposed by the authors, we hoped that after the ozonolysis of **1.200**, water would intercept the carbonyl oxide **1.276** and convert it into **1.277** which should collapse to intermediate dialdehyde **1.275** (Scheme 1.91). Gratifyingly, application of this protocol to **1.200** gave a product **1.278**, which was presumably a complex mixture of aldehyde hydrates **1.279** based on analysis of LCMS data (Scheme 1.92). Due to the complexity of the ¹H NMR spectrum of **1.279**, we were unable to fully characterize it.

Scheme 1.91: Proposed mechanism for the ozonolysis with dissolved water

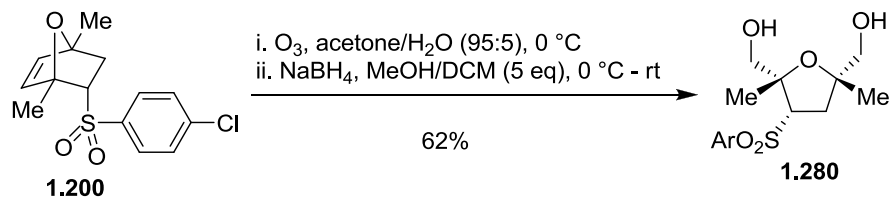


Scheme 1.92: First successful oxidative cleavage



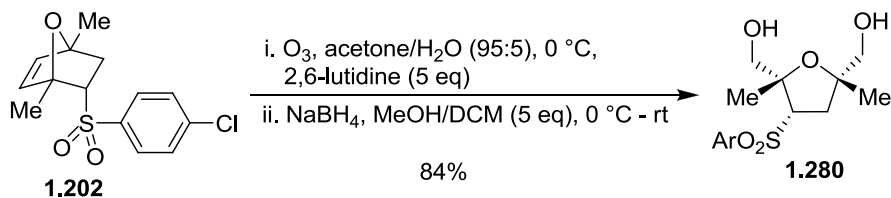
Encouraged by this result, oxabicyclo **1.200** was then subjected to ozonolysis, followed immediately by a reductive workup with sodium borohydride to give tetrahydrofuran **1.280** in 62% yield over two steps (Scheme 1.93).

Scheme 1.93: Two-step oxidation and reduction sequence to give diol **1.280**

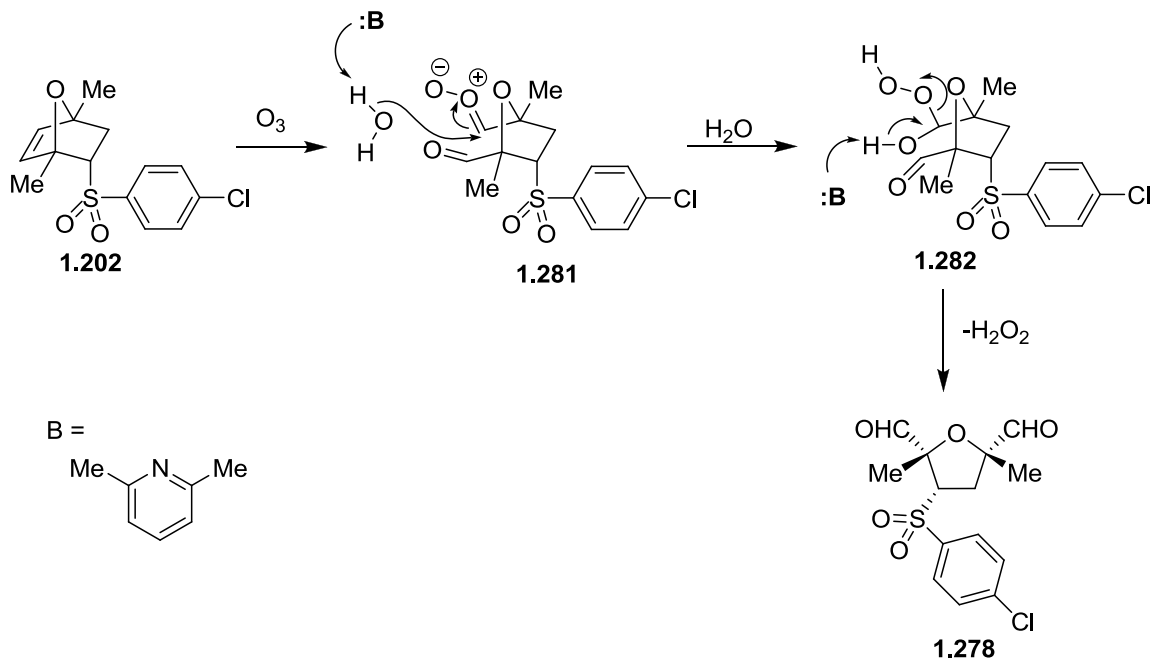


We subsequently found that ozonolysis of **1.200** in the presence of 2,6-lutidine improved the yield of the diol **1.280** from 62% to 84% (Scheme 1.94). The reasons for this improvement are still unclear, but we believe that the lutidine may function as a general base promoting the addition of water to the carbonyl oxide **1.281**, leading to intermediate **1.282** (Scheme 1.95). Alternatively, 2,6-lutidine may also facilitate the breakdown of the intermediate secondary ozonide **1.282** to give dialdehyde **1.278** by release of hydrogen peroxide.

Scheme 1.94: Addition of 2,6-lutidine improves oxidation yield

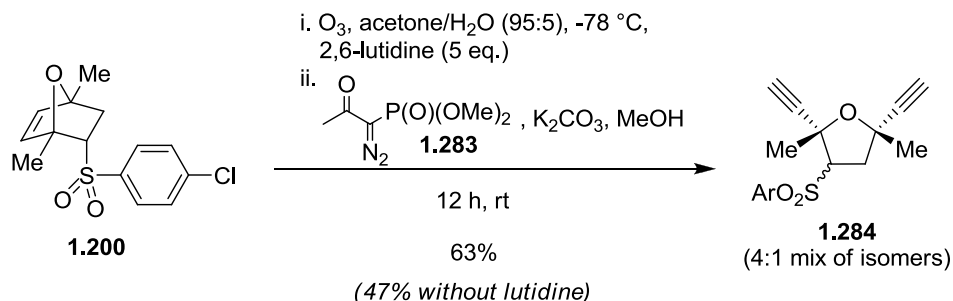


Scheme 1.95: Possible mechanistic explanations for the improved yield with base



We were also interested in the conversion of dialdehydes such as **1.278** into their corresponding diyne *via* the Ohira-Bestmann reaction. The inspiration for this transformation was from our planned route to cortistatin A.⁸ In the event, ozonolysis of **1.200** followed by a double Ohira-Bestman reaction using dimethyl-1-diazo-2-oxopropylphosphonate (**1.283**) delivered the di-yne **1.284** in 63% yield over two steps (Scheme 1.96). The sulfonyl group epimerized under prolonged exposure to base, giving **1.284** as a mixture (4:1) of isomers. When the oxidation was performed without 2,6-lutidine, the yield over two steps was only 47%. At this point, we had developed two successful modes for the ring-opening cycloadducts such as **1.200**, and our attention turned to the cleavage of the sulfone auxiliary.

Scheme 1.96: Oxidation followed by Ohira-Bestmann reaction sequence

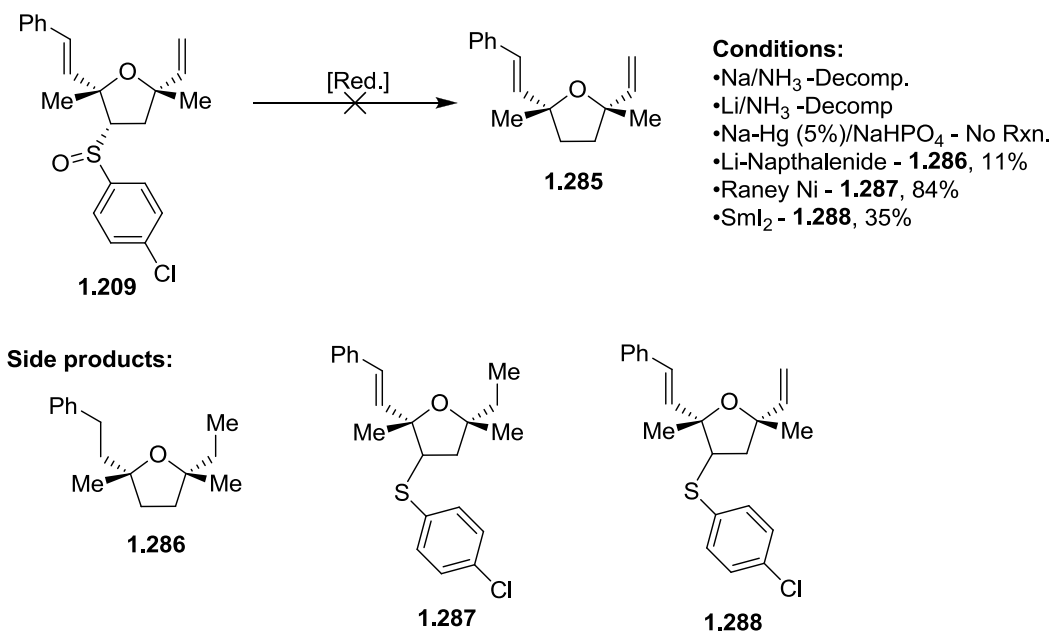


1.5. CLEAVAGE OF THE SULFONE AUXILIARY

Early explorations into the reductive cleavage of the carbon-sulfur bond were focused upon the sulfoxide substituted tetrahydrofuran **1.209**, after attempts to remove the sulfur from the oxabicyclic systems were unsuccessful. We attempted the reductive cleavage of **1.209** by submitting it to a variety of well-known conditions (Scheme 1.97).^{89,95} However, all attempts to prepare tetrahydrofuran **1.285** from **1.209** were unsuccessful, and no trace of the desired product was ever detected. The conditions that were attempted are summarized in Scheme 1.96. The dissolving metal reductions with sodium or lithium in ammonia led to a mixture of unidentifiable products. Na/Hg amalgam failed to react with **1.209**, leading to only recovered starting material.⁹⁰ When **1.209** was exposed to lithium-naphthalenide, only trace amounts of over-reduced **1.286** were isolated, along with an intractable mixture of side-products.⁹¹ Exposure of **1.209** to deactivated Raney nickel resulted in the reduction of the unsubstituted olefin, along with partial reduction of the sulfoxide giving tetrahydrofuran **1.287** in 84% yield.⁹² Reducing

1.209 with an excess of SmI_2 gave partially reduced thioether **1.288** in 35% yield, along with a mixture of unidentified side products.^{93,94}

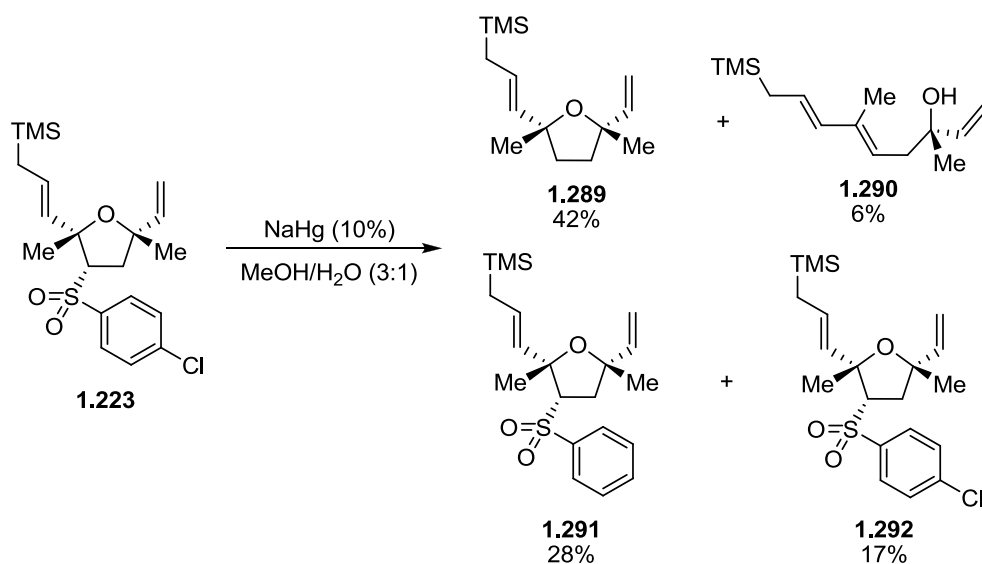
Scheme 1.97: Attempts at reductive cleavage of sulfoxide **1.209**



We then examined the reductive cleavage of the sulfone moiety from **1.223**. We chose this specific substrate because it was readily available in high yield, and, we believed the TMS group would be stable under harsh reductive conditions, thus limiting the possible side products. The screening began with a survey of known reductive conditions for arylsulfonyl groups.⁹⁵ A large number of reagents were tested, including dissolving metal reductions with sodium or lithium, samarium diiodide, and metal-mercury amalgams. Each reagent was examined using a range of solvents, temperatures, and pH's (Scheme 1.98). Unfortunately, all of the conditions failed to convert **1.223** to the desired product **1.289** in yields higher than 10% or simply gave no reaction at all.

Numerous attempts under many conditions were made to improve the yield of the desulfurization using either Na-Hg amalgam and Mg/MeOH. Fortuitously, while examining various additives, we found that the addition of a small amount of water to methanol dramatically improved the yield of **1.289** when using Na-Hg amalgam (Scheme 1.99). A number of products were isolated from the reaction, including the desired product **1.289** in 42% yield, ring-opened material **1.290** in 6% yield, dehalogenated material **1.291** in 28% yield, and 17% of recovered starting material **1.292**.

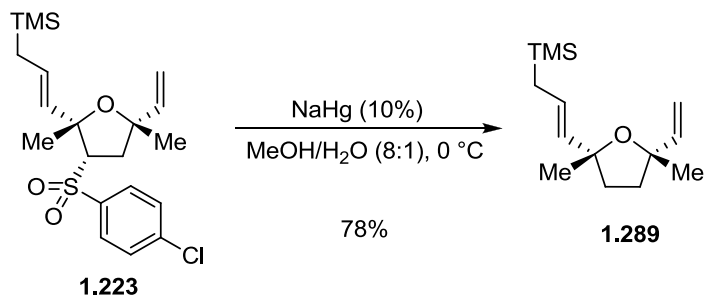
Scheme 1.99: Distribution of products with sodium amalgam in wet methanol



Having isolated and characterized the side products, we began to search for optimal conditions to give **1.289**. After extensive optimization, we found that use of Na-Hg (10%) in a MeOH/H₂O (8:1) at 0 °C gave the desulfurized product **1.289** in 78% yield (Scheme 1.100). All attempts to run the reaction in a buffered solution failed to improve

yields. Upon development of conditions for the cleavage of the sulfone, our methodology could now access the desired tetrahydrofuran substructure **1.1**.

Scheme 1.100: Optimized desulfurization conditions

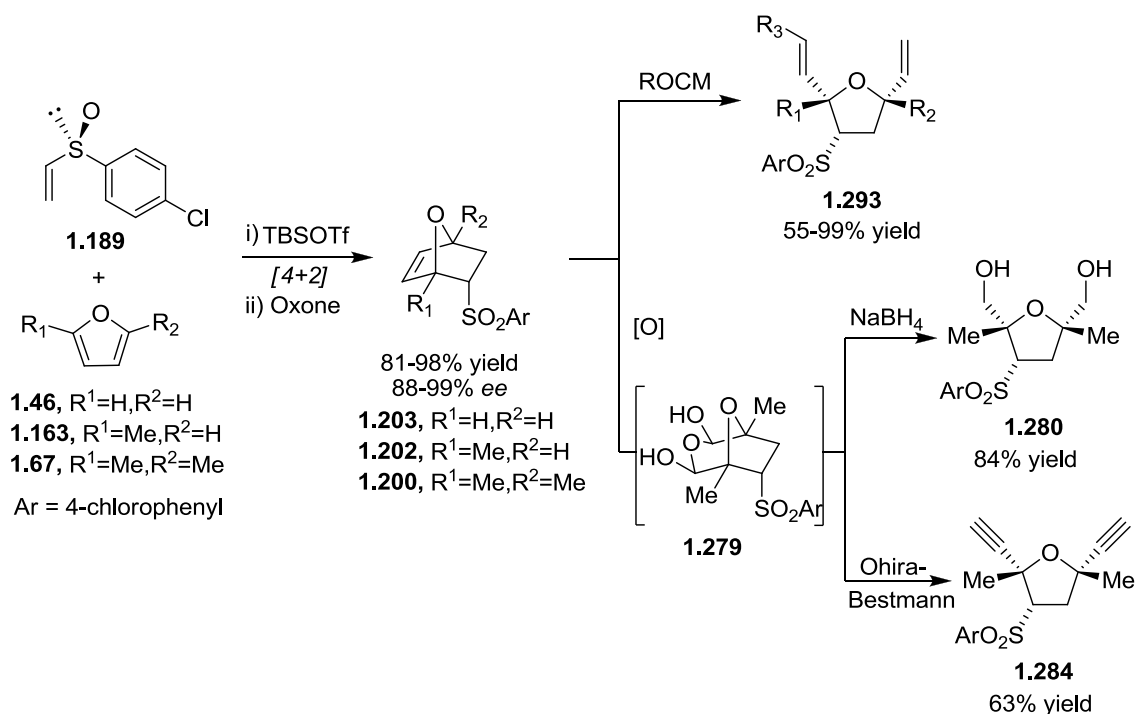


1.5. SUMMARY AND CONCLUSIONS

In summary, we have discovered a novel chiral vinyl sulfoxide **1.191**, which is readily available in both enantiomeric forms, that undergoes highly diastereoselective [4+2] cycloadditions with several substituted furans. This discovery represents the first examples of the use of substituted furans in enantioselective [4+2] cycloadditions with vinyl sulfoxides. Additionally, vinyl sulfoxide **1.191** reacts with furan in the presence of TBSOTf in higher yield and diastereoselectivity than any previously reported chiral vinyl sulfoxide. A one-pot cycloaddition/oxidation sequence represents a useful synthetic tool, which adds diversity to the vinyl sulfoxide dienophile by allowing facile conversion to the sulfone. The cycloadducts obtained from the reaction of **1.191** with furans **1.46**, **1.163**, or **1.67** may be further processed *via* several different refunctionalization

manifolds, including a highly regioselective ring-opening cross metathesis or an ozonolysis in the presence of water to give facile access to 2,2,5-tri- and 2,2,5,5-tetrasubstituted tetrahydrofurans, represented by **1.293**, **1.280**, and **1.284**. These heterocycles comprise structural subunits in a broad array of biologically active natural products. A general summary of the method is summarized below in Scheme 1.101.⁹⁶

Scheme 1.101: Summary of the enantioselective cycloaddition and ring-opening reactions



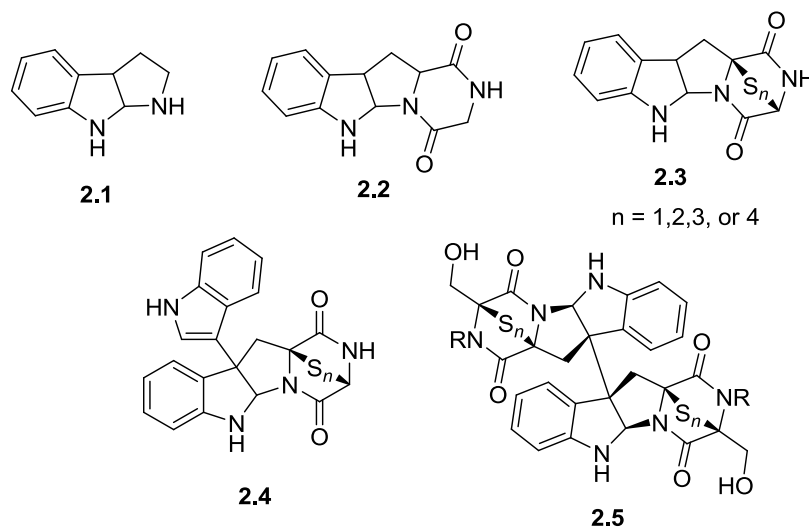
Chapter 2: Synthesis of diketopiperazine containing natural products

2.1. INTRODUCTION TO DIKETOPIPERAZINE CONTAINING ALKALOIDS

2.1.1. Hexahydropyrroloindoline diketopiperazine alkaloids biological activity and structure

Hexahydropyrroloindoline alkaloids are a large family of secondary fungal metabolites that contain interesting structural features and exhibit a wide range of potent biological activities.⁹⁷ Members of this class of natural products all contain a common tricyclic core structure represented by **2.1** (Figure 2.1). Many of these alkaloids possess an additional cyclic dipeptide diketopiperazine substructure, represented by tetracycle **2.2**. A particularly bioactive class of these compounds contains a bridged polysulfide linkage across the cyclic dipeptide diketopiperazine substructure as is illustrated by **2.3**.⁹⁸ The polysulfide linker can range from one to four sulfur atoms in length. Some of the toxicity of these sulfur containing molecules is attributed to the polysulfide bridge of the diketopiperazine subunit, which can either conjugate directly to cysteine residues or generate reactive oxygen intermediates.⁹⁹ Molecules containing this polysulfide bridge are commonly referred to as epipolythiodiketopiperazine (ETP) alkaloids.

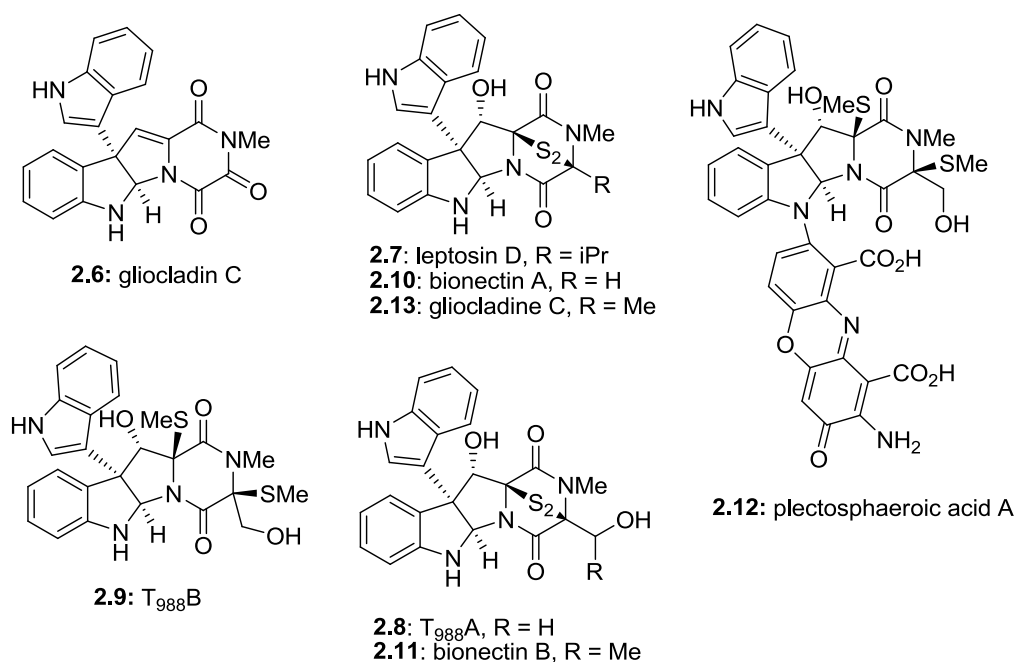
Figure 2.1: Common core structures of hexahydropyrroloindoline alkaloids



Most ETP-containing hexahydropyrroloindoline natural products have either a 3-indole substituted core such as **2.4** or a symmetrical dimeric structure shown by **2.5**. Many hexahydropyrroloindoline natural products are thought to be biosynthetically derived from two molecules of tryptophan or tryptophan-containing peptides.¹⁰⁰ Natural products such as **2.4** and **2.5** have attracted considerable interest from the synthetic community in recent years due to their promising and unique bioactivities, and their challenging molecular architectures.¹⁰¹ For instance gliocladin C (**2.6**)¹⁰² and leptosin D (**2.7**)¹⁰³, are cytotoxic against P-388 lymphocytic leukemia cell lines with ED₅₀ values of 240 ng/mL and 86 ng/mL, respectively (Figure 2.2).¹⁰⁴ Similarly, T988 A (**2.8**) and T988 B (**2.9**) exhibit cytotoxicity against P-388 cell lines with ED₅₀ values of 0.25 µg/mL and 2.18 µg/mL, respectively.¹⁰⁵ Bionectins A (**2.10**) and B (**2.11**) exhibit antibacterial activity against methicillin-resistant *S. aureus* (MRSA) and quinolone-resistant *S. aureus* (QRSA) with MIC = 10-30 µM/mL.¹⁰⁶ The novel alkaloid plectosphaeroic acid A (**2.12**) is an inhibitor of indoleamine 2,3-dioxygenase (IDO), which is a promising target for

removing the ability of cancer cells to escape immunologically mediated cellular rejection.^{107,108} Plectosphaeroic acid A (**2.12**) inhibited recombinant human IDO with an IC_{50} of 2 μ M/mL. The cinnabarinic acid side-chain appears to be important to its unique bioactivity.¹⁰⁹

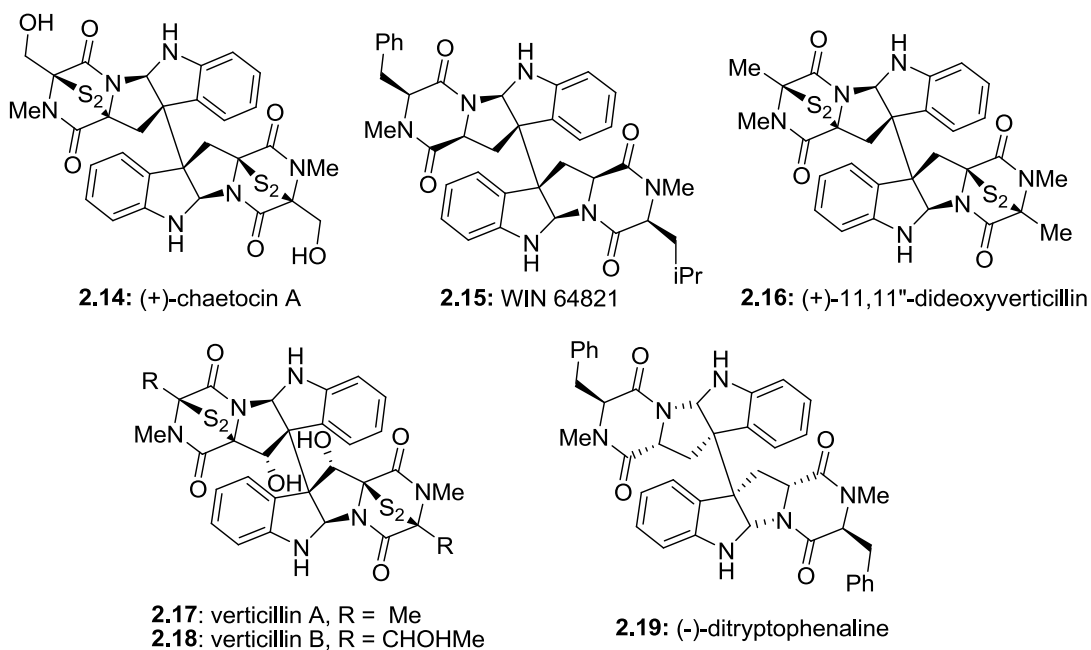
Figure 2.2: 3-indole substituted hexahydropyrroloindoline natural products



Among the symmetrical, dimeric ETPs, chaetocin (**2.14**) has been one of the more synthesized natural products due to its early isolation, and wide-ranging bioactivity (Figure 2.3).¹¹⁰ Not only does it possess potent antibacterial and cytostatic activity,¹¹¹ but **2.14** is also known to be a potent inhibitor of histone methyl transferases (HMTs), enzymes that play important roles in controlling gene expression.¹¹² WIN 64821 (**2.15**) is a competitive substance-P antagonist with sub-micromolar potency against the human

NK1 receptor,¹¹³ and it is also an antagonist of the cholecystinin type-B receptor.¹¹⁴ Dideoxyverticillin (**2.16**) has significant inhibitory activity against topoisomerases I and II, and it exhibits cytotoxicity toward a number of human cancer cell lines.¹¹⁵ Both verticillins A (**2.17**) and B (**2.12**), along with ditryptophenaline (**2.19**) exhibit antimicrobial activity against Gram-positive bacteria and potent antitumor activity in HeLa cell lines.^{116,117}

Figure 2.3: Symmetrical dimeric hexahydropyrroloindoline containing natural products



Given the powerful biological activities of nearly all hexahydropyrroloindoline natural products, they have attracted significant attention from synthetic chemists.^{101,118} While a number of innovative synthesis of these and related natural products have been reported, our goal was to develop a novel route that enabled rapid access to many

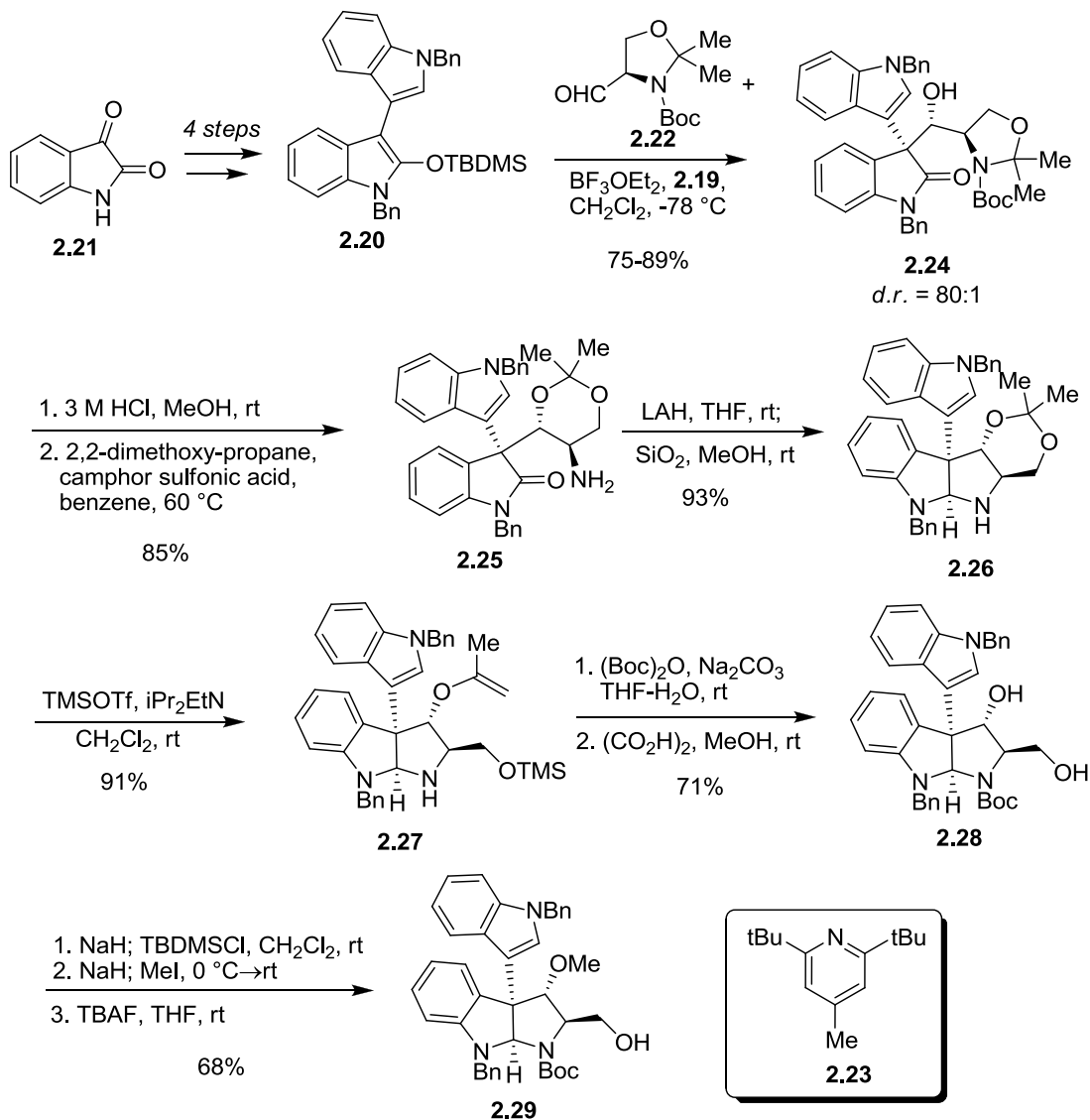
members within this family.^{119,120} In addition, we sought a route that would have the potential to access the entire family of natural products and for the synthesis of analogues for biological screening.¹²¹ We selected plectosphaeroic acid A (**2.12**) and T998 A (**2.8**) and B (**2.9**) as our initial targets because they have not yet been synthesized, and we targeted gliocladin C (**2.6**) as it may be an intermediate in the route to **2.8** and **2.9**.

2.1.2. Previous synthetic studies toward hexahydropyrroloindoline diketopiperazine natural products

2.1.2.1. Overman's first total synthesis of gliocladin C

The first total synthesis and structural confirmation of gliocladin C (**2.6**) was published in 2007 by Overman and co-workers.¹²² Their synthesis began with a diastereoselective Mukaiyama aldol reaction between 2-siloxyindole **2.20**, which is available in four steps from isatin (**2.21**), and the serine derived aldehyde **2.22** in the presence of BF₃OEt₂ and 4-methyl-di-*tert*-butylpyridine (**2.23**) to give key intermediate **2.24** in 75-89% yield as a mixture (80:1) of diastereostereomers (Scheme 2.1). The oxazoline and Boc protecting groups were then cleaved under acidic conditions, and the resultant diol was protected using 2,2-dimethoxypropane to provide 1,3-dioxane **2.25**. Reduction of **2.25** with LAH₄ and ionization of the hemiaminal with silica gel gave aminal **2.26** in 93% yield. TMSOTf activated rearrangement of the dimethylketal of **2.26** gave the protected primary alcohol **2.27** in 91% yield. Protection of the amine with Boc-anhydride followed by deprotection gave diol **2.28**. Further functional group manipulations allowed for the conversion of the secondary alcohol to the methyl ether **2.29** in 68% yield over three steps.

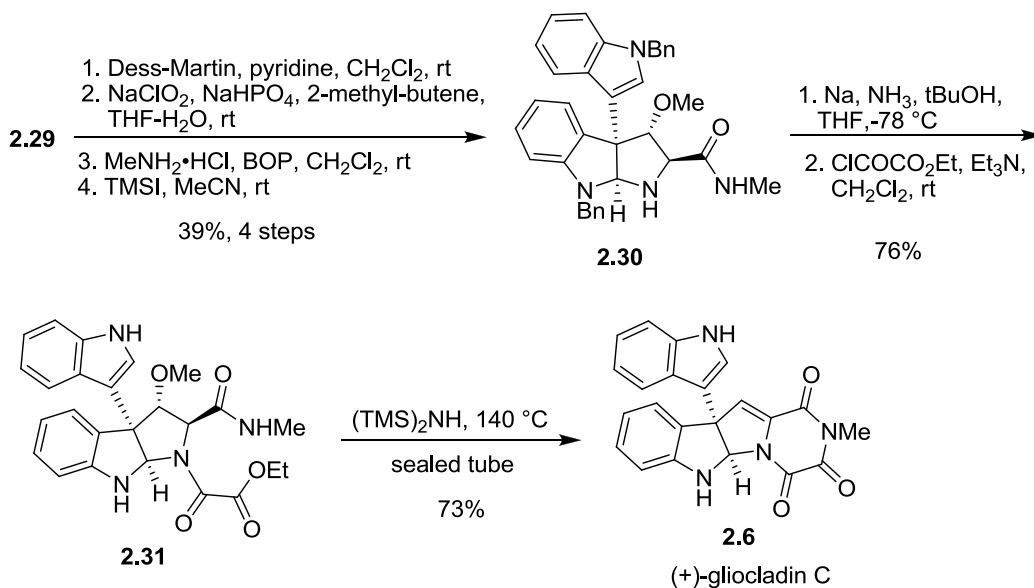
Scheme 2.1: Overman's total synthesis of gliocladin C



The primary alcohol **2.29** was then oxidized to a carboxylic acid that was coupled with methylamine, and the Boc group was removed to provide the amide **2.30** in 39% yield over four steps (Scheme 2.2). Deprotection of the benzyl groups under reductive conditions, followed by acylation gave oxalyl ester **2.31**. This precursor was then heated

in a sealed tube with hexamethyldisilazane to furnish (+)-gliocladin C (**2.6**) in 73% yield. Additionally, the central step of the sequence featured an asymmetric Mukaiyama aldol reaction for the construction of the quaternary carbon of **2.24**.

Scheme 2.2: Completion of Overman's synthesis of gliocladin C

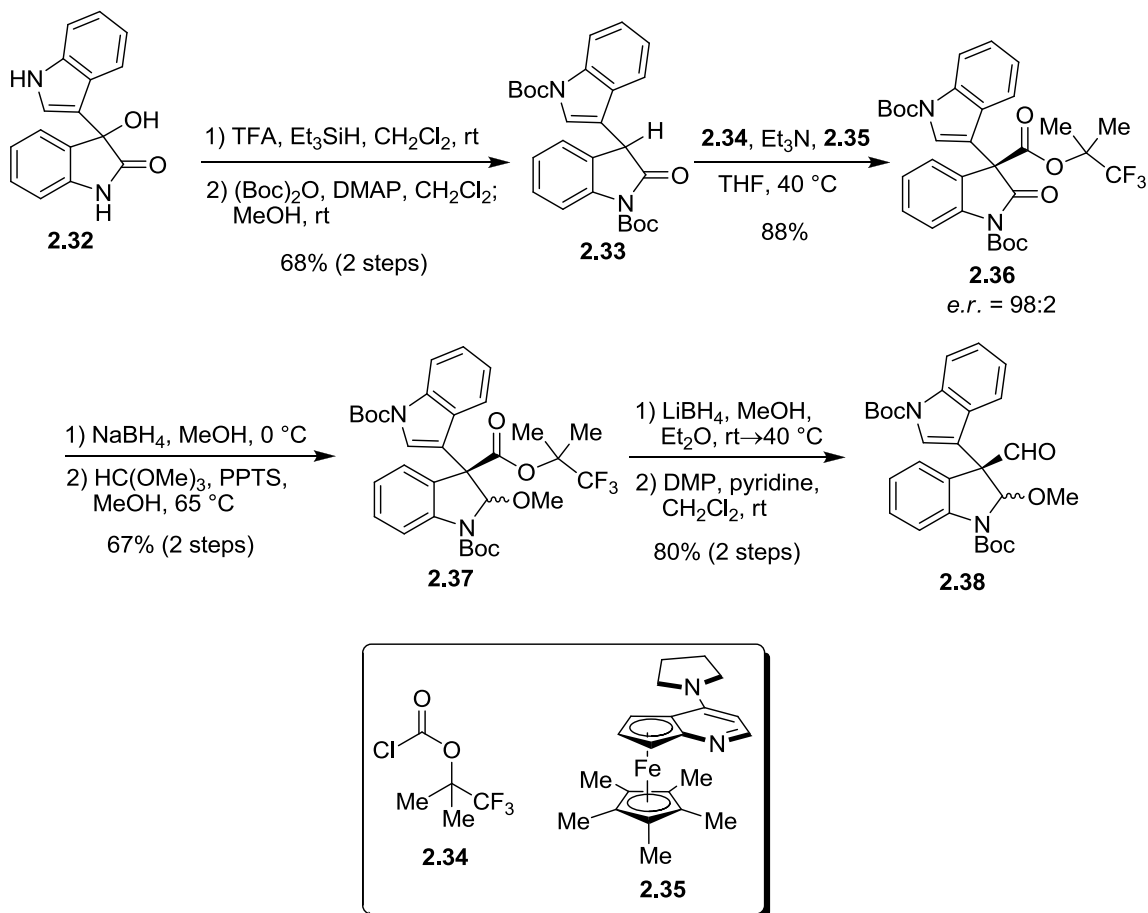


2.1.2.2. Overman's second generation approach to gliocladin C

As a follow-up to their 2007 total synthesis, Overman, DeLorbe, and co-workers shortened their route to gliocladin C (**2.6**) by assembling the molecule in a more convergent manner.¹²³ Beginning with oxindole **2.32**, which was available in one step from isatin and indole, the alcohol was reduced by exposure to acid in the presence of triethylsilane (Scheme 2.3). Protection of the intermediate using Boc-anhydride, gave oxindole **2.33** in 68% yield over two steps. In the next step, stereoinduction was introduced by acylation with 2,2,2-trichloro-1,1-dimethylethyl chloroformate (**2.34**),

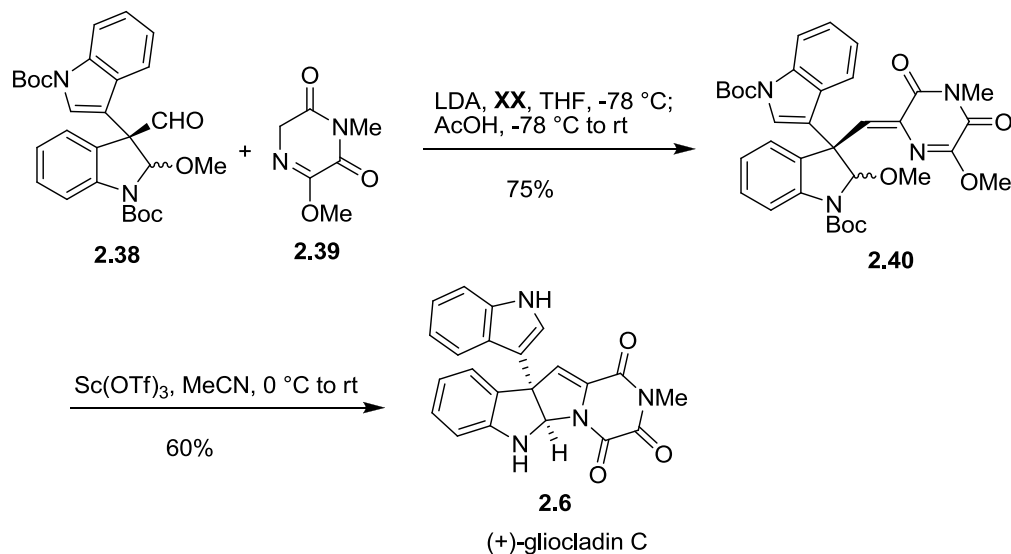
followed by a Lewis acid catalyzed O→C rearrangement catalyzed by 5 mol % of Fu's (S)-(-)-4-pyrrolidinopyrindinyl-(pentamethylcyclopentadienyl) iron catalyst **2.35**. This asymmetric rearrangement leads to enantioenriched 3,3-disubstituted oxindole **2.36** in 88% yield and a 98:2 enantiomeric ratio.¹²⁴ The oxindole carbonyl group was then selectively reduced to the hemi-aminal with sodium borohydride and converted to **2.37** in 67% yield over two steps using trimethylorthoformate. A two-step reduction/oxidation sequence with lithium borohydride and Dess-Martin periodinane gave access to intermediate aldehyde **2.38**, which constitutes the left half of the glicladin C (**2.6**).¹²⁵

Scheme 2.3: Overman's second generation synthesis of gliocladin C



The trioxopiperazine nucleophile **2.39** was deprotonated with lithium diisopropylamide, and the intermediate anion was allowed to react with aldehyde **2.38** to provide **2.40** in 75% yield (Scheme 2.4). Exposure of **2.40** to Sc(OTf)₃ in acetonitrile at room temperature delivered gliocladin C (**2.6**) in 60% yield. This approach constituted the most concise synthesis of gliocladin C to date and featured a novel asymmetric rearrangement to access enantioenriched 3,3-disubstituted oxindole **2.36**. Furthermore, the base induced coupling of **2.38** and **2.39** exemplifies their convergent approach to the hexahydropyrroloindoline natural products

Scheme 2.4: Completion of the enantioselective synthesis of (+)-gliocladin C

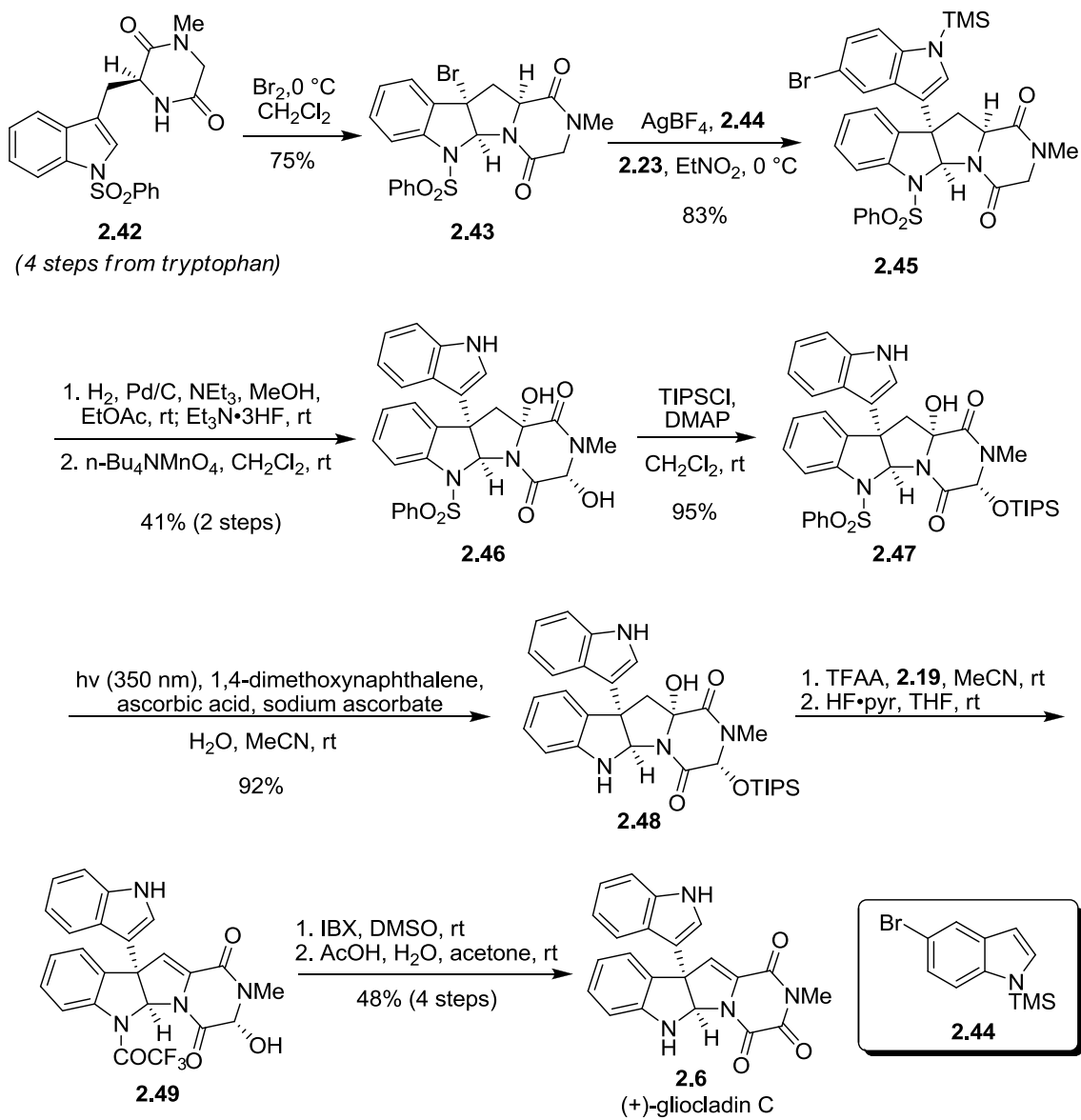


2.1.2.3. Movassaghi's total synthesis of gliocladin C

Recently Movassaghi and co-workers published a concise total synthesis of (+)-gliocladin C (**2.6**) and the related natural product gliocladin B (Scheme 2.5).¹²⁶ The route commences with the bromocyclization of diketopiperazine **2.42**, which was synthesized in four steps from tryptophan, to give tetracycle **2.43** in 75% yield. Ionization of the bromine with AgBF_4 in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (**2.23**) followed reaction with the bromoindole **2.44** gave the core structure **2.45** in good yield. Nucleophile **2.44** was used because it provided **2.45** in the highest yield during an extensive screening of a variety of substituted indoles, but reasoning for this yield enhancement was provided. Removal of the extraneous indole bromide functionality, followed by oxidation of the diketopiperazine ring gave the somewhat unstable **2.46** in 41% yield over two steps. No reason for the stereoselectivity was given. Selective protection of the less hindered alcohol gave silyl ether **2.47**, and then removal of the *N*-

sulfonyl protecting group under buffered photolytic conditions furnished **2.48** in excellent yield.¹²⁷ The aryl amine was protected with trifluoroacetic anhydride that occurred with concomitant elimination of the tertiary alcohol, fluoride promoted removal of the TIPS-group with HF•pyridine gave **2.49**. Oxidation of the secondary alcohol of **2.49** and removal of the *N*-protecting group gave (+)-gliocladine C in 48% yield over four steps. This synthetic strategy featured a novel Friedel-Crafts-based coupling of **2.43** and indole **2.44**. Furthermore it featured a stereoselective bis-oxidation of diketopiperazine **2.45** using *n*Bu₄NMnO₄.

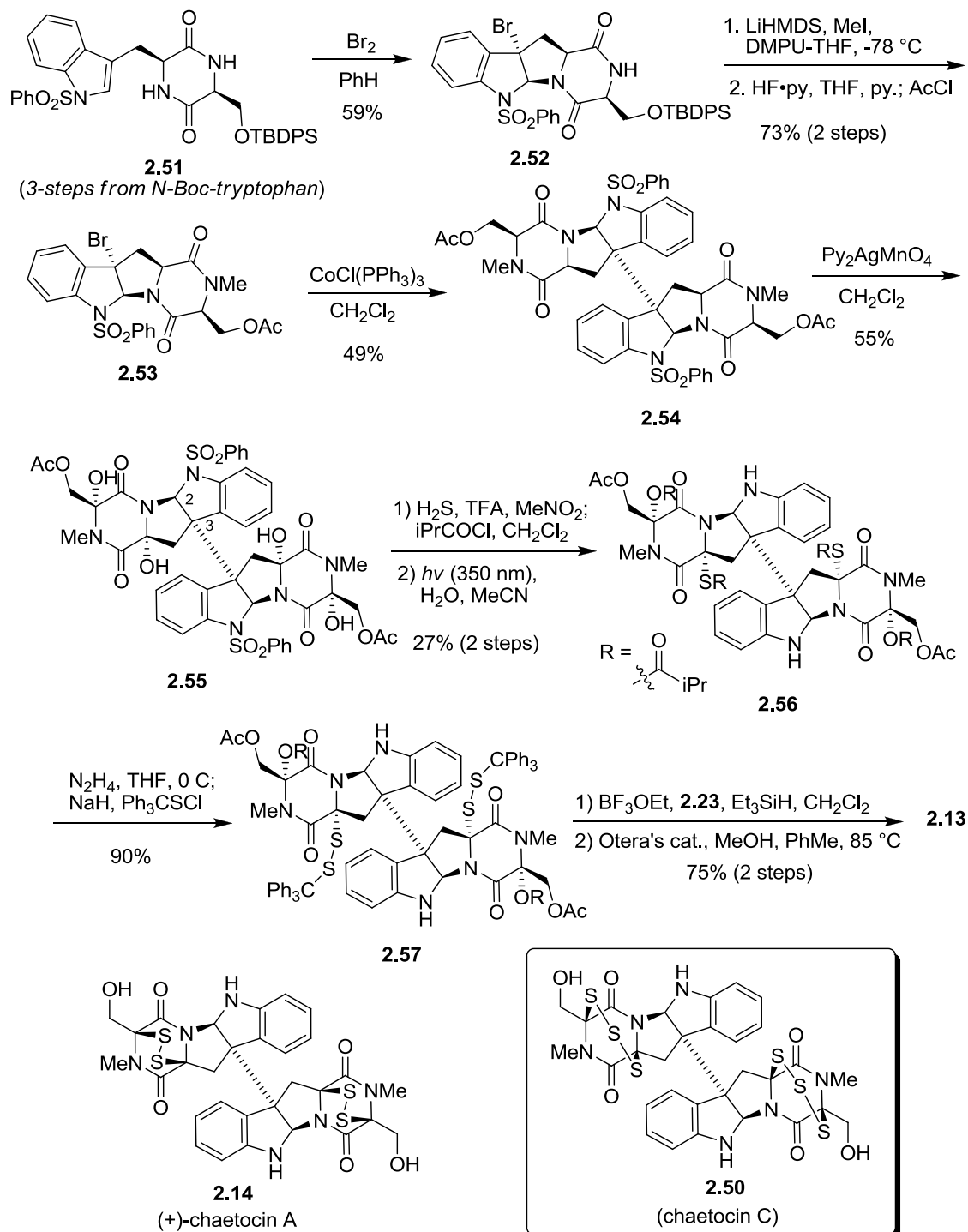
Scheme 2.5: Movassaghi's total synthesis of gliocladin C



2.1.2.4. Chaetocin A

Movassaghi and co-workers have published a highly stereoselective route to the dimeric alkaloids epipolythiodiketopiperazines chaetocin A (**2.13**) and C (**2.50**)¹²⁸ as well as dideoxyverticillin A (**2.15**).¹²⁹ This synthesis of **2.6** began with the bromine-induced cyclization of tryptophan-derived diketopiperazine **2.51**, which was synthesized in three steps from *N*-Boc-tryptophan and serine methyl ester (Scheme 2.6), to give **2.52**. The tetracycle was *N*-methylated followed by removal of the silicon. *O*-acylation of the intermediate led to **2.53** in 73% yield. The CoCl(PPh₃)₃-mediated reductive radical dimerization of **2.53** provided the dimeric diketopiperazine **2.54** in 49% yield. The dimer was then oxidized to tetraol **2.55** with Py₂AgMnO₄ in 55% yield and subsequent exposure of tetraol **2.56** to trifluoroacetic acid and hydrogen sulfide generated a bisthiohemiaminal intermediate, which was then exposed to isobutrylchloride to acylate the free alcohols and thiols. The stereoinduction is suggested to be directed by the approach of the oxidant from the less hindered face of the molecule. Following photolytic deprotection of the *N*-sulfonyl group, they isolated advanced intermediate **2.56** in 27% yield over two steps.

Scheme 2.6: Movassaghi's total synthesis of chaetocin A



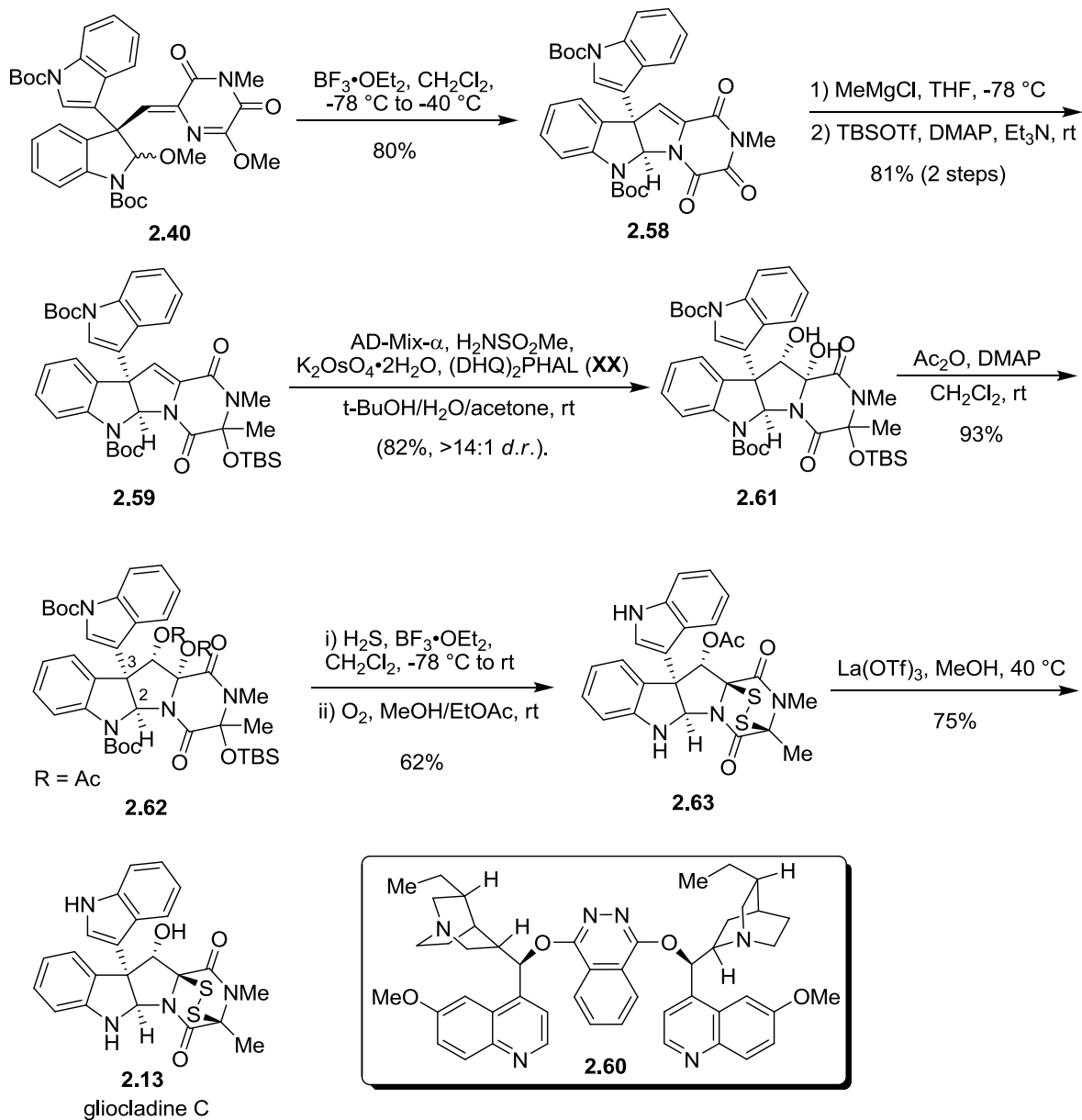
The free thiols were revealed by a hydrazinolysis of thioesters, which were then sulphenylated to give **2.57** in 90% yield. Subsequent ionization of the isobutyrate and efficient cyclization with concomitant loss of a triphenylmethyl cation produced the bis-acetylated precursor to the natural product. Deprotection using Otera's catalyst and methanol gave chaetocin A (**2.14**) in 75% yield over the two steps.¹³⁰ This total synthesis of (+)-chaetocin A represents an innovative approach to the dimeric epipolythiodiketopiperazine alkaloids. The route featured a novel cobalt catalyzed dimerization of bromide **2.53** and a challenging stereoselective manganese tetrahydroxylation of **2.54**. The stepwise construction of these sulfur-bridged diketopiperazine represents a novel and versatile method for the installation of the disulfide and trisulfide bridges.

2.1.2.5. Gliocladin C

As an extension of their synthesis of gliocladin C (**2.6**) (*vide supra*), Overman and co-workers prepared the closely related epidithiodioxopiperazine gliocladin C (**2.13**).¹²³ The synthesis branched from intermediate **2.40** with the BF₃OEt₂ induced ring-closure and concomitant dimethylation to provide the tetracyclic structure **2.58** in 80% yield (Scheme 2.7). Trioxopiperazine-fused pyrrolidinoindoline **2.58** was reacted with methylmagnesium chloride at -78 °C, and the free alcohol was protected with TBSOTf to give a mixture of siloxy epimers **2.59** in 81% yield. Catalytic dihydroxylation of the internal olefin using AD-mix- α gave diol **2.61** in 82% yield with good diastereoselectivity. Use of AD-mix- β resulted in poorer diastereoselectivity. Protection of the diol with acetic anhydride and DMAP provided diacetate **2.62** in 93% yield. This

intermediate was then exposed to hydrogen sulfide and BF_3OEt_2 under ionizing conditions in a sealed tube, followed by exposure to oxygen to deliver the disulfide **2.63** in 62% yield. It was suggested that the selectivity was due to the approach of sulfur to the less sterically encumbered face of the molecule. The addition of both thiols to the same face of the diketopiperazine ring was first documented by Kishi and co-workers, and it was suggested to be due the first thiol directing of the approach of second hydrogen sulfide molecule by hydrogen bonding.¹³¹ Deprotection with methanolic $\text{La}(\text{OTf})_3$ gave (+)-gliocladiene C (**2.13**) in 75% yield. This work featured the first total synthesis of gliocladiene C (**2.13**), and it featured a diastereoselective dihydroxylation and innovative Lewis acid catalyzed sulfur installation. It should be noted that this synthesis was published during our ongoing total synthesis of this natural product.

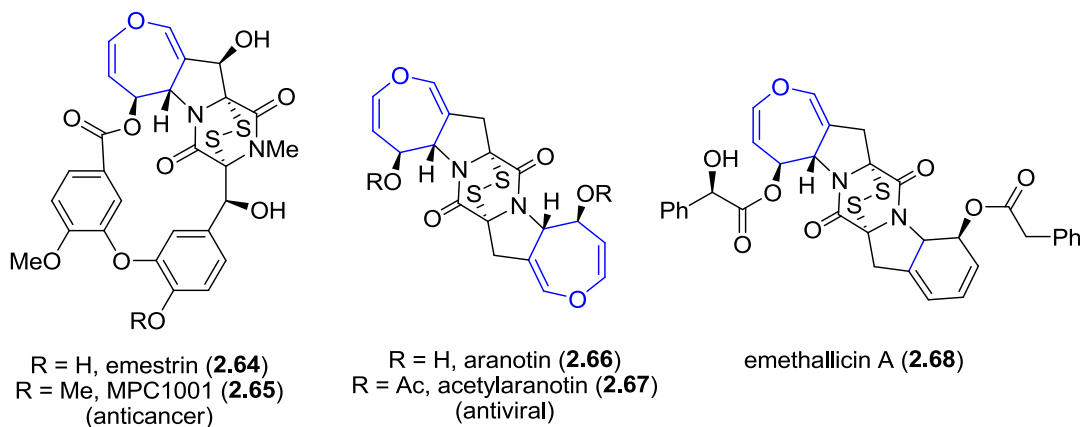
Scheme 2.7: Overman's total synthesis of (+)-gliocladiine C



2.1.3. Dihydrooxepine epidithiodiketopiperazine natural products structure and biological activity.

The oxepin moiety is a common substructure in a number of biologically active natural products.^{132,133} There have been a number of methods reported regarding the synthesis of these seven-membered heterocycles.¹³⁴ There is a specific subset of biologically potent oxepin containing alkaloids known as dihydrooxepine epidithiodiketopiperazine containing natural products (Figure 2.4). These compounds are characterized by the presence of a 4,5-dihydrooxepine ring and a sulfur-bridged epidithiodiketopiperazine, both of which are linked *via* a pyrrolidine ring. Included among the most potent of these compounds are emestrin (**2.64**),¹³⁵ MPC1001 (**2.65**),¹³⁶ aranotin (**2.66**), acetylaranotin (**2.67**),¹³⁷ emethallicin A (**2.68**).¹³⁸

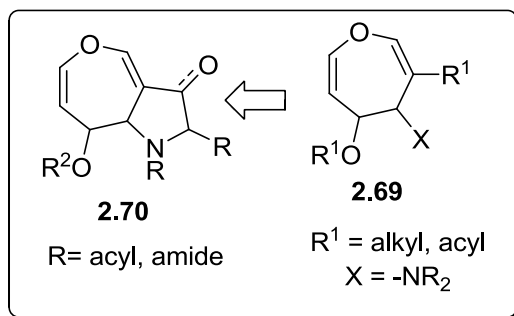
Figure 2.4: Dihydrooxepine epidithiodiketopiperazine containing natural products.



Compounds **2.64-2.68** exhibit an impressive array of biological activities, ranging from inhibition of viral RNA polymerases¹³⁹ to antiproliferative¹³⁶ and apoptotic activity against various human cancer cell lines.¹⁴⁰ MPC1001(**2.65**) shows some of the most

potent anticancer properties with in vitro activity against the DU145 prostate cancer cell line with an IC_{50} value of 9.3 nM. The complex structure and impressive anticancer activity of these alkaloids make them attractive synthetic targets. Despite this, acetylaranotin (**2.66**) has been the only member of the dihydrooxepine epidithiodiketopiperazine class of natural products to have been synthesized.¹⁴¹ When exploring the potential for the total synthesis of MPC1001, we discovered that there was a paucity of methodology to access dihydrooxepine cores, such as the ones present in structures **2.64-2.68**. This lack methodology inspired our interest in the development of methodology for the construction of the dihydrooxepin core, specifically those substituted only at the 3-, 4-, and 5-carbon atoms, as shown by **2.69** (Figure 2.5), because we wished to create a route that would be directly applicable toward the synthesis of the core structure of dihydrooxepine ETP alkaloids, represented by **2.70**.

Figure 2.5: Dihydrooxepine target structure and ETP natural product core structure

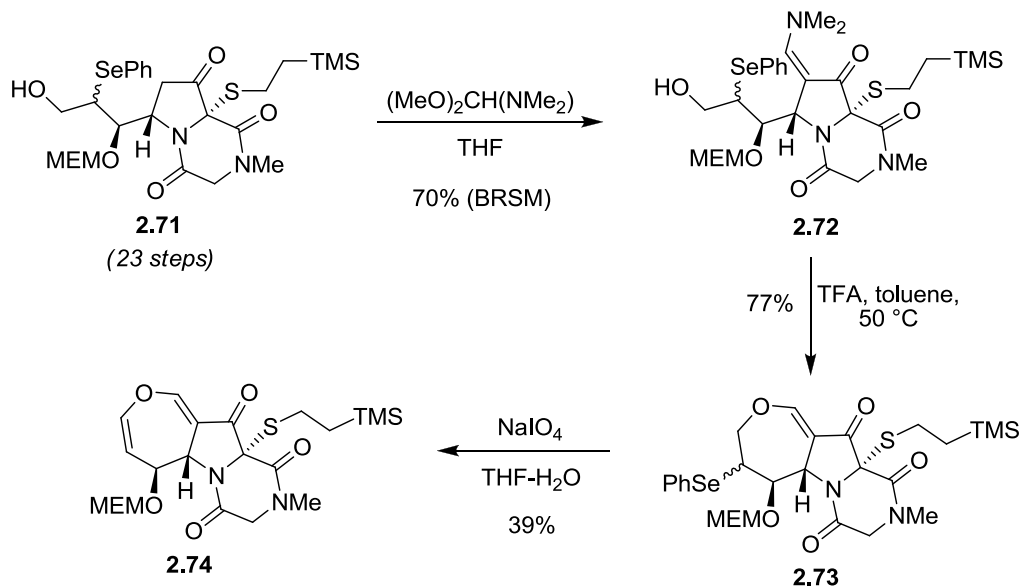


2.1.4. Synthetic methods to access substituted 4,5-dihydrooxepins

2.1.4.1. Stepwise ring construction using nucleophilic ring-closure and elimination

A survey of the literature revealed a limited number of methods for the construction of 4,5,6-substituted dihydrooxepines such as **2.69**. One such technique involves the stepwise construction of the oxepin core structure by the intramolecular cyclization of 1,6-ene-ol or 1,6-yne-ol, giving the seven-membered oxepin ring. A surrogate leaving group was then eliminated to reveal the final dihydrooxepin structure. This stepwise approach was reported by Clive and co-workers in their synthesis of the AB ring system of MPC1001 **2.65** (Scheme 2.8).^{142,143} Their late stage intermediate **2.71** was first elaborated to the vinylogous amide **2.72** in 70% yield using dimethylformamide dimethyl acetal in THF. The intramolecular cyclization was induced upon exposure to trifluoroacetic acid in toluene, to provide the oxepin ring **2.73** in 77% yield. Selenoxide oxidation and elimination with sodium periodate furnished the dihydrooxepin **2.74** in 39% yield.

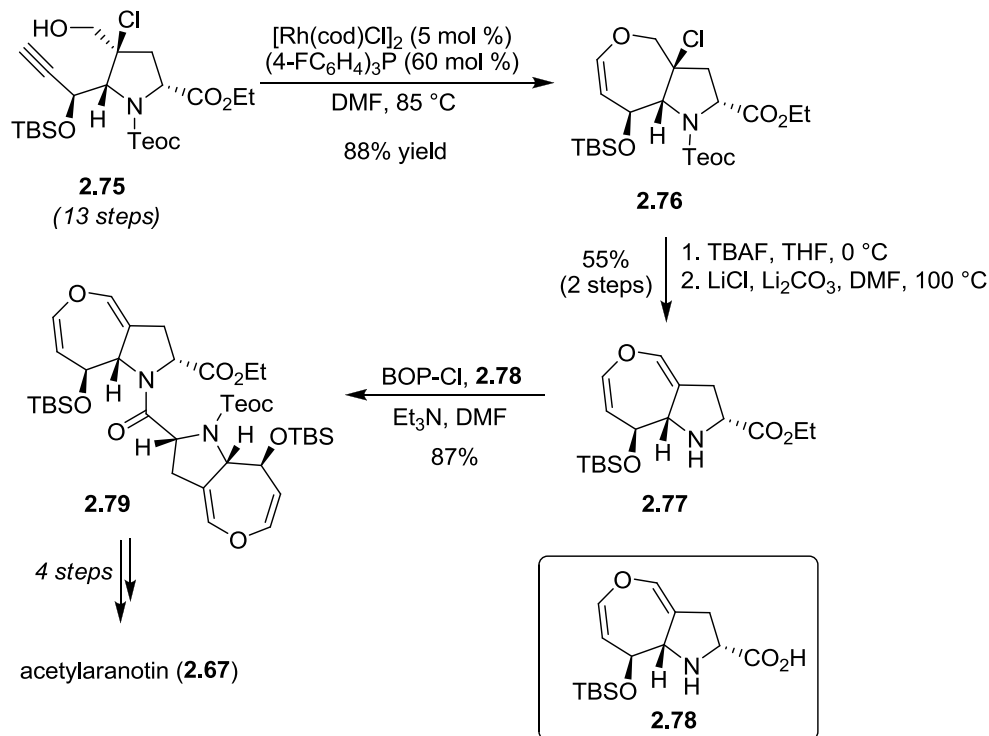
Scheme 2.8: Clive's approach to the MPC1001 core structure



A similar oxacyclization was used by the Reisman lab in their total synthesis of acetylaranotin (**2.67**) (Scheme 2.9).¹⁴¹ Starting from advanced yneol **2.75**, they successfully applied a rhodium-catalyzed cycloisomerization to create the oxepine **2.76** in 88% yield. Sequential protecting group removal with TBAF, followed by elimination using lithium carbonate afforded the dihydrooxepine **2.77** in 55% yield over two steps. A peptide coupling with related amino acid **2.78** using standard coupling conditions yielded 87% of dimer **2.79**, which was elaborated to acetylaranotin (**2.67**) in four steps. This synthesis is the only total synthesis of a dihydrooxepine epidithiodiketopiperazine natural product. While both Clive's synthesis of **2.74** and Reisman's synthesis of **2.67** by oxacyclization successfully accessed core structures such as **2.70**, each did so at the cost of a long and complicated sequence to prepare the requisite starting material preparation.

We aimed to design a method that avoids the synthesis of complex starting materials in order to reduce the overall step count.

Scheme 2.9: Synthesis of the dihydrooxepine core of acetylaranotin

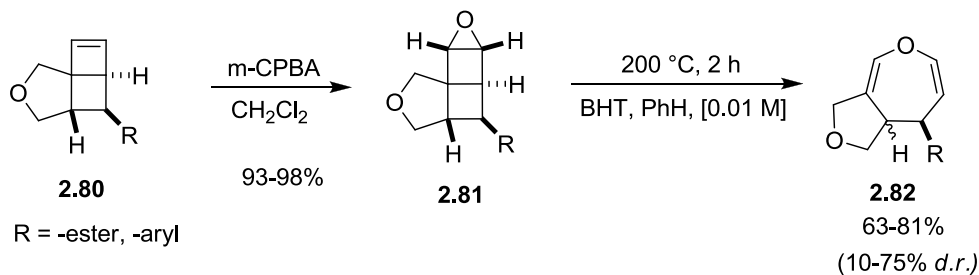


2.1.4.2. Epoxidation of cyclobutenes and ring expansion to oxepins

The Snapper group reported the synthesis of functionalized bicyclic oxepins by a thermal rearrangement of highly strained cyclobutanes (Scheme 2.10).¹⁴⁴ Epoxidation of cyclobutene **2.80** using meta-chloroperoxybenzoic acid (m-CPBA) gave the tetracycle **2.81** in 93-98% yield. Heating **2.81** in benzene at 200 °C in a sealed tube furnished bicyclic oxepins **2.82** in 63-81% yield as mixtures of diastereomers. This method was

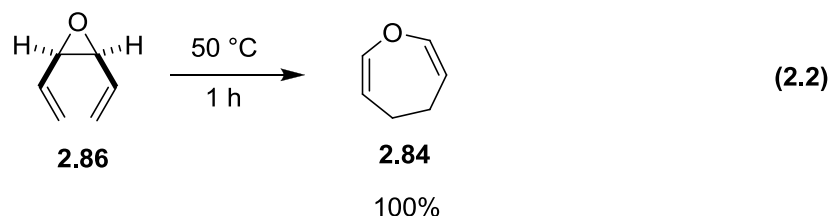
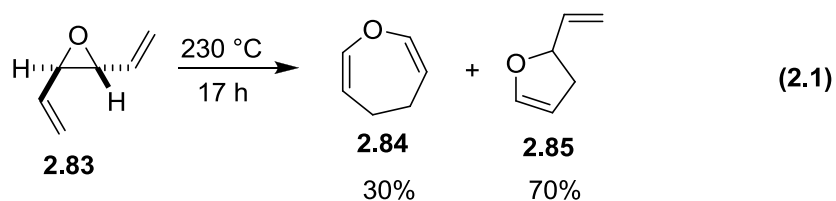
limited substrate scope to only ester or aryl R-groups and diastereoselectivity tended to be low (9-75%).

Scheme 2.10: Ring expansion of strained cyclobutanes



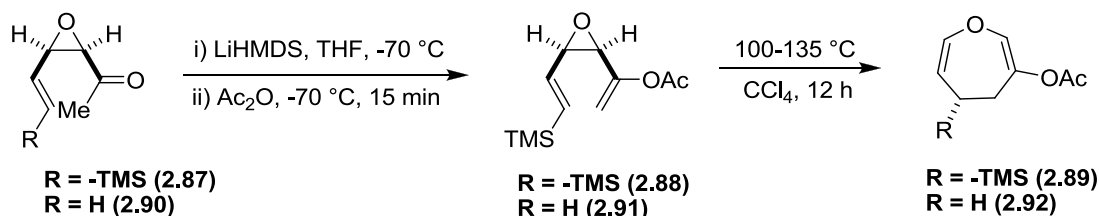
2.1.4.3. Constructions of oxepins by Cope rearrangement of divinyl epoxides

One attractive approach to oxepins is features the Cope rearrangement of divinyl epoxides.¹⁴⁵ White and co-workers initiated a four-carbon ring expansion of *trans*-divinyloxirane **2.83** at 230 °C to give partial conversion to 4,5-dihydrooxepine (**2.84**) in 30% conversion along with dihydrofuran **2.85** in 70% conversion (equation 2.1).¹⁴⁶ Notably, they discovered that the *trans*-divinyl epoxide **2.86** underwent complete conversion to oxepine **2.84** at 50 °C (equation 2.2), no trace of furan **2.85** was detected. It has been suggested that this difference in reactivity between cis-epoxide **2.86** and trans-epoxide **2.3** is due to a favorable orbital overlap for the ring expansion to the seven-membered ring.¹⁴⁷



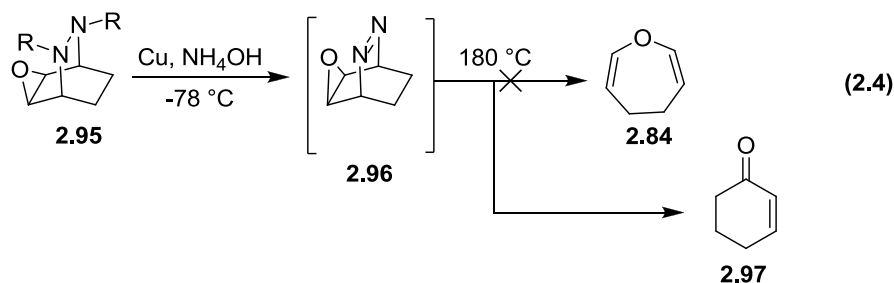
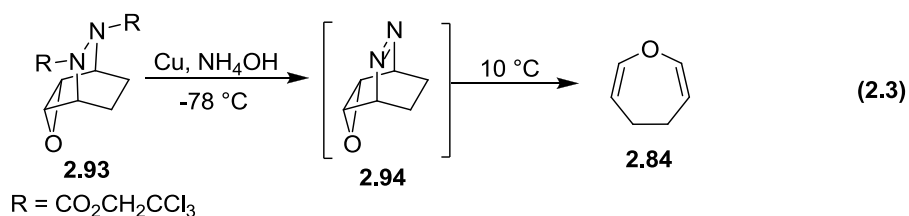
The Cope rearrangement of substituted *cis*-2,3-divinyl epoxides was also explored by the White lab.¹⁴⁸ They reported the synthesis of 4,6-disubstituted dihydrooxepins by first constructing methyl ketone substituted vinyl epoxide **2.87**, which they converted to the *trans*-substituted enol derivative **2.88** by kinetic deprotonation and acylation with acetic anhydride (Scheme 2.11). Divinyl epoxide **2.88** underwent the Cope rearrangement to give oxepin **2.89** after 12 hours at 135 °C. When using a *cis*-2,3-divinyl epoxide **2.91**, which lacks substitution at the terminus of the diene, the rearrangement required only 100 °C to generate oxepine **2.92** in 80% yield. They proposed that the additional substituent added steric strain to the transition state. Furthermore, they found that the *trans*-isomers related to **2.88** and **2.91** did not undergo any reaction at temperatures as high as 180 °C. The Cope rearrangement of divinyl epoxides has never been applied in the context of a total synthesis, possibly due to the lack of methodology to access *cis*-divinyl epoxides.

Scheme 2.11: Synthesis of substituted dihydrooxepins by Cope rearrangement



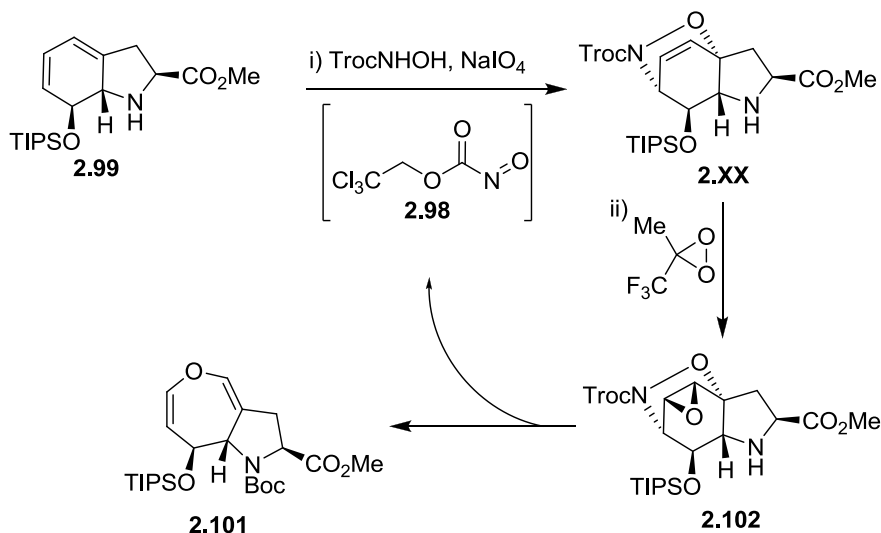
2.1.4.4. Oxepin synthesis via the retro-homo Diels-Alder reaction of epoxides

White and co-workers reported a novel approach to the dihydrooxepin core by a retro-homo Diels-Alder reaction driven by the extrusion of nitrogen gas. The *endo*-epoxide **2.93** was synthesized by a cycloaddition between benzene oxide and bis(trichloroethyl)azodicarboxylate,¹⁴⁹ followed oxidation using copper in ammonium hydroxide to reveal the diaza-oxotricyclononene intermediate **2.94** (equation 2.3). The strained intermediate **2.94** was warmed to 10 °C, whereupon nitrogen gas was liberated revealing 4,5-dihydrooxepin (**2.84**) as the sole product. In contrast, *exo*-epoxide **2.95** was converted to **2.96**, which was easily handled at room temperature (equation 2.4). This intermediate was found to be thermally stable up to 180 °C, at which point **2.96** rearranged to the undesired cyclohexanone **2.97**. This reaction is presumed to occur through a radical pathway due to poor orbital overlap for the desired retro homo-Diels-Alder.



Nicolaou and co-workers applied the retro-homo Diels-alder oxepin construction to their synthesis of the monomeric unit of aranotin **2.66** (Scheme 2.12).¹⁵⁰ They used trichloroethyl nitrosoformate (**2.98**), which was generated from TrocNHOH and NaIO₄, as the dienophile and bicyclic diene **2.99**, to give cycloadduct **2.100**. Oxidation of **2.100** with methyl(trifluoromethyl)dioxirane afforded the oxepin core structure **2.101** in 40% yield. The reaction was assumed to proceed through fleeting intermediate **2.102**, which rapidly underwent a retro-homo Diels-Alder cyclization and regenerated dienophile **2.98**. The use of retro-homo Diels-Alder cycloadditions is a promising candidate for the synthesis of substituted oxepins; however, the necessity to use *endo*-epoxides renders the construction of the starting materials challenging.

Scheme 2.12: Application of the retro-Diels-Alder/epoxide opening.



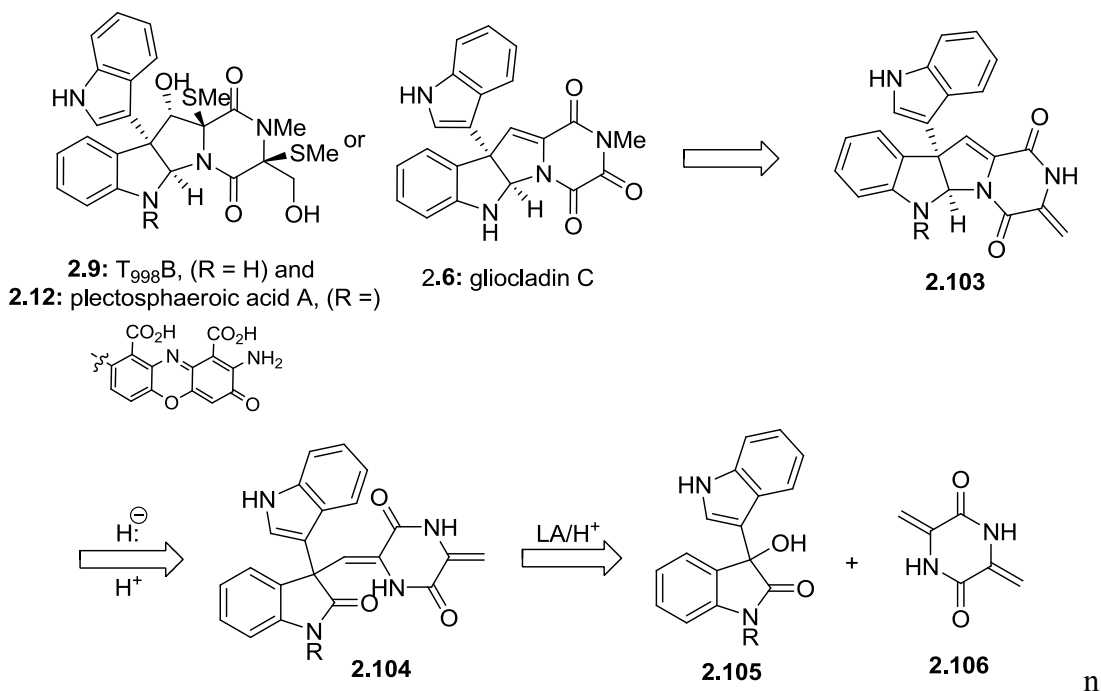
2.2. PROPOSED ROUTES TOWARD DIKETOPIPERAZINE CONTAINING NATURAL PRODUCTS AND PRECEDENT

2.2.1. Retrosynthesis of hexahydropyrroloindoline diketopiperazine alkaloids

We envisioned a route to access several hexahydropyrroloindoline natural products that was both concise and novel. We chose to target T998B (**2.9**) and plectosphaeroic acid A (**2.12**), because these alkaloids have never before been synthesized despite their promising bioactivities. A total synthesis of these natural products would serve as a useful tool for further exploration of their interesting biological properties by way of analogue synthesis. Furthermore, we saw an opportunity to access gliocladin C (**2.6**), which has been synthesized by several groups.^{123,126} A more concise synthesis of gliocladin C would serve to showcase the efficiency and generality of our proposed route.

Our original retrosynthetic analysis of **2.9**, **2.12**, and **2.6** led to the diene core structure **2.103** (Scheme 2.13). We envisioned this substructure a branching point, wherefrom we could either access epidithiodiketopiperazine alkaloids such as **2.7-2.12** or simpler hexahydropyrroloindoline alkaloids, such as **2.6**. The hexacyclic core **2.103** would arise from the intramolecular reductive ring-closure of oxindole **2.104**, 3,3-disubstituted oxindole **2.104** would arise using an ionic coupling of hydroxyoxindole **2.105** and didehydro diketopiperazine **2.106**.

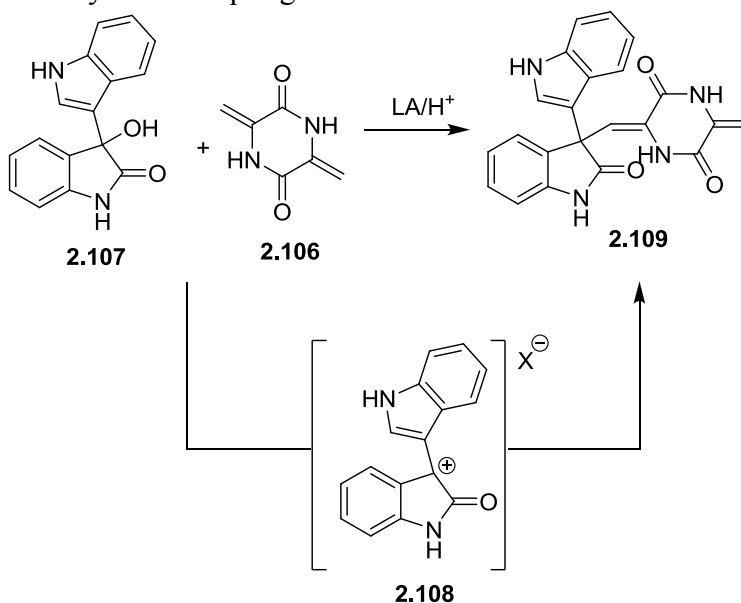
Scheme 2.13: Retrosynthetic analysis of **2.9**, **2.12**, and **2.6**



The key step involves the ionization of 3-hydroxyoxindole **2.107** under Lewis acidic conditions, leading to the cationic intermediate **2.108**, which would then be

trapped by the enamide¹⁵⁴ functionality of diketopiperazine **2.107** and to provide the oxindole **2.109** (Scheme 2.14). Use of a dehydrodiketopiperazine as a nucleophile has very little precedent, and it has never been used in total synthesis.¹⁵¹ Thus, our initial focus will be the development of this coupling. Upon validation of this step, we envisioned that an asymmetric variant could be developed using either a chiral Lewis or Brønsted acid.

Scheme 2.14: Key ionic coupling between π -cation **2.108** and nucleophile **2.106**



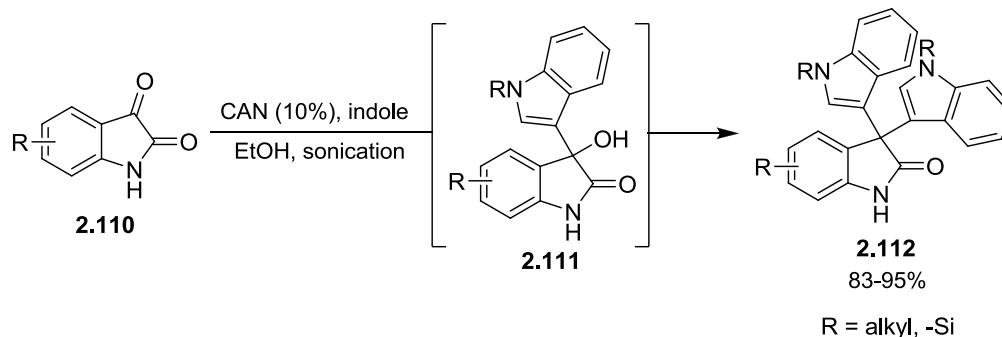
2.2.2. Precedent for the synthesis of hexahydropyrroloindoline alkaloids

2.2.2.1. Ionization and nucleophilic capture of 3-hydroxyoxindoles

The crucial transformation of **2.107** to **2.109** was inspired by a number of literature reports involving the ionization and nucleophilic capture of 3-hydroxy-

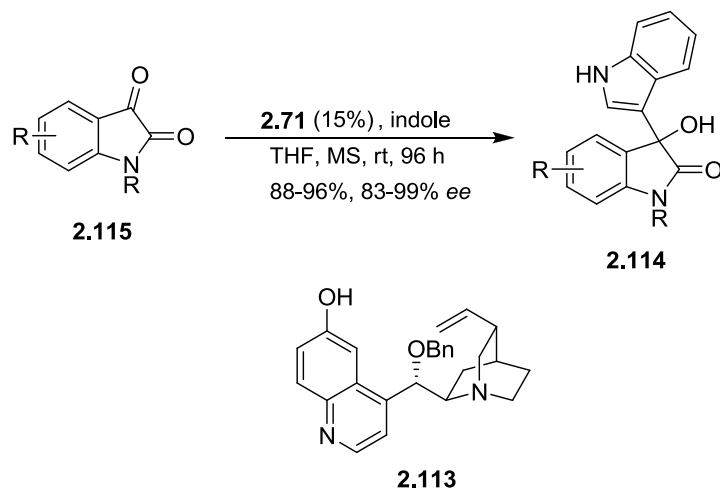
indolylinolin-2-ones. These reactive substrates are generally synthesized by the nucleophilic addition of an indole to isatin. For example, Ji and Wang found that ceric ammonium nitrate efficiently catalyzed the reaction of isatins **2.110** with indoles (Scheme 2.15).¹⁵¹ The cerium was thought to act as a Lewis acid that activated the isatin carbonyl group toward nucleophilic attack by π -nucleophiles such as indole, to give intermediate **2.111**. The alcohol moiety **2.111** then ionized to generate a cation that was quenched with a second equivalent of indole, giving disubstituted oxindoles such as **2.112** in 83-95% yield.

Scheme 2.15: Cerium catalyzed double addition of indole to isatin



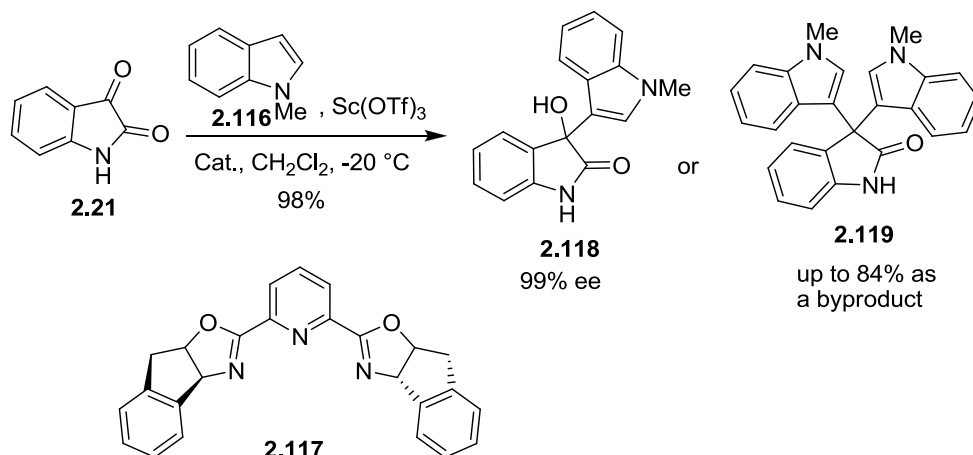
The asymmetric addition of indole to isatin has recently been reported by Chimni and co-workers,¹⁵² who describe the use of cinchona alkaloid-derived catalysts such as **2.113** to catalyze the formation of 3-hydroxyoxindoles **2.114** by the addition of indole into isatin derivatives such as **2.115** (Scheme 2.16). The enantioselective addition proceeded in excellent yields and enantioselectivities. The ability to control the enantioselectivity at the 3-position of oxindoles with chiral ligands is relevant to our own plans because of our design of an enantioselective route.

Scheme 2.16: Bifunctional cinchona alkaloid controlled asymmetric addition to isatins



Further promising developments came from the lab of Franz and co-workers,¹⁵³ who treated isatin **2.21** to *N*-methylindole (**2.116**) in the presence of scandium triflate or copper triflate and chiral ligand **2.117** to form 3-hydroxyoxindole **2.118** in 98% yield and 99% enantiomeric excess (Scheme 2.17). If the reaction is warmed above -20 °C they observed a second ionization of **2.118** to give the disubstituted oxindole **2.119** in 84% yield. These results suggest that we might be able to use a chiral Lewis-acid to control the addition of diketopiperazine nucleophile **2.106** to our proposed 3-hydroxy oxindole intermediate **2.107**.

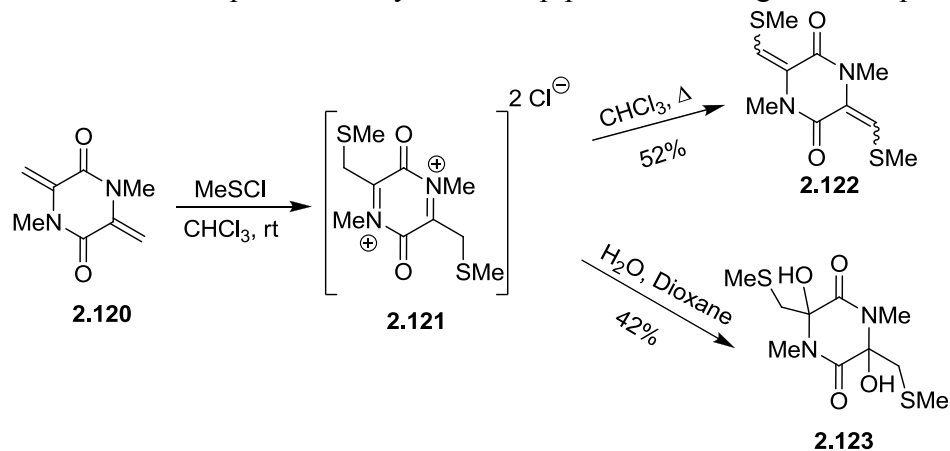
Scheme 2.17: Chiral Lewis acid controlled synthesis of 3-hydroxyoxindoles



2.2.2.2. Nucleophilic attack using didehydro diketopiperazines

A much less precedented step in our route is the use of unsaturated diketopiperazines as nucleophiles. There is very limited information regarding the reactivity of the enamide functionality of unsaturated diketopiperazines such as **2.106**. To our knowledge, the closest literature precedent comes from Matsunari and co-workers,¹⁵⁴ who explored the reactivity of bis-unsaturated diketopiperazine **2.120** under a variety of conditions. For example, methyl chlorosulfide reacted with the enamide groups of **2.120** leading to the putative iminium salt **2.121**, which either underwent elimination to give **2.122** in 52% yield, or reaction with H_2O to afford diol **2.123** in 42% yield (Scheme 2.18).

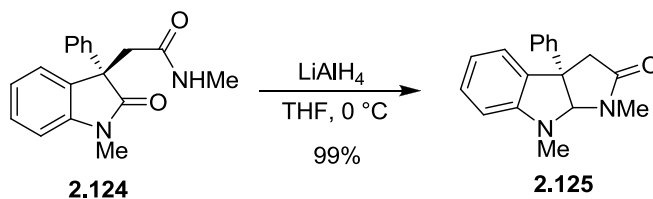
Scheme 2.18: Rare example of di-dehydro diketopiperazines acting as nucleophiles



2.2.2.3. Intramolecular reductive ring closure

The intramolecular reductive ring closure of an oxindole with a pendant amide function is a well preceded procedure.¹⁵⁵ Stoltz has shown that methyl amide **2.124** may be reduced with lithium aluminum hydride in THF to give pyrrolidinoindoline **2.125** (Scheme 2.19).¹⁵⁶ No over reduction of the amide carbonyl group was reported.

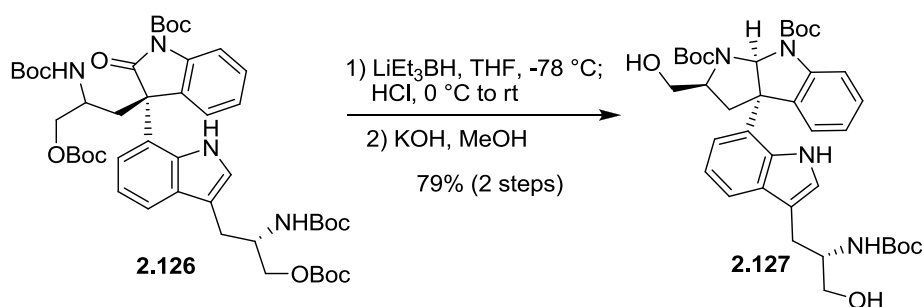
Scheme 2.19: Reduction of methyl amide to the tricyclic aminal with LiAlH_4



Similarly, in their total synthesis of asperazine, Overman and co-workers demonstrated an effective intramolecular reductive coupling of the Boc-protected amine **2.126** (Scheme 2.20).¹⁵⁷ Namely, reduction of the oxindole carbonyl group with lithium

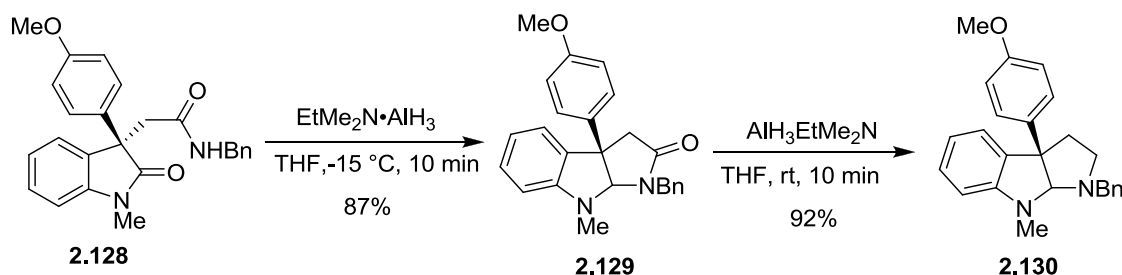
triethylborohydride furnished an intermediate that underwent acid catalyzed cyclization to give the pyrrolidine ring. Selective cleavage of the carbonates yielded **2.127** in 79% yield over two steps.

Scheme 2.20: Two-step reductive coupling with lithium triethylborohydride and HCl



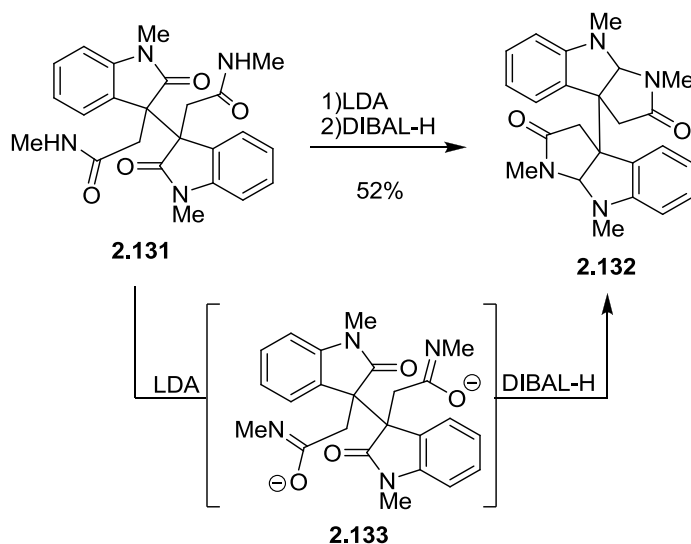
Buchwald and co-workers synthesized 3,3-disubstituted oxindoles, such as **2.128**, by a palladium-catalyzed arylation/alkylation sequence.¹⁵⁸ When **2.128** was reduced with alane-dimethylethylamine complex, pyrroloindoline cores like **2.129** were obtained (Scheme 2.21). Control of temperature was critical, because over reduction to **2.130** can occur if the reaction was performed at room temperature.

Scheme 2.21: Buchwald's use of alane-dimethylethylamine complex



Another example of this type of cyclization was reported by Rodrigo and co-workers in their total synthesis of folicanthine.¹⁵⁹ Although **2.131** could not be converted to **2.132** under a variety of the standard conditions, they discovered that deprotonation of **2.131** with lithium diisopropylamide to give dianion **2.133**, followed by reduction gave **2.132** in 52% yield (Scheme 2.22).

Scheme 2.22: Sequential de-activation of reactive free-amides and reductive coupling

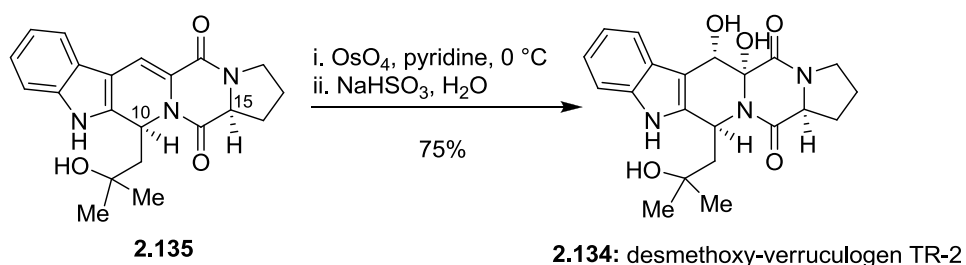


2.2.2.4. Oxidation of the internal enamide double bond

We proposed a late stage oxidation of the internal olefin of the hexacyclic pyrroloindoline **2.103**, leading to our final targets **2.6**, **2.9**, and **2.12** (Scheme 2.8). The most applicable precedent for this transformation is from the aforementioned total synthesis of (+)-gliocladrine C **2.13** by Overman and co-workers (Scheme 2.7).¹²³ Additional precedent is found in the report of the total synthesis of the mycotoxin

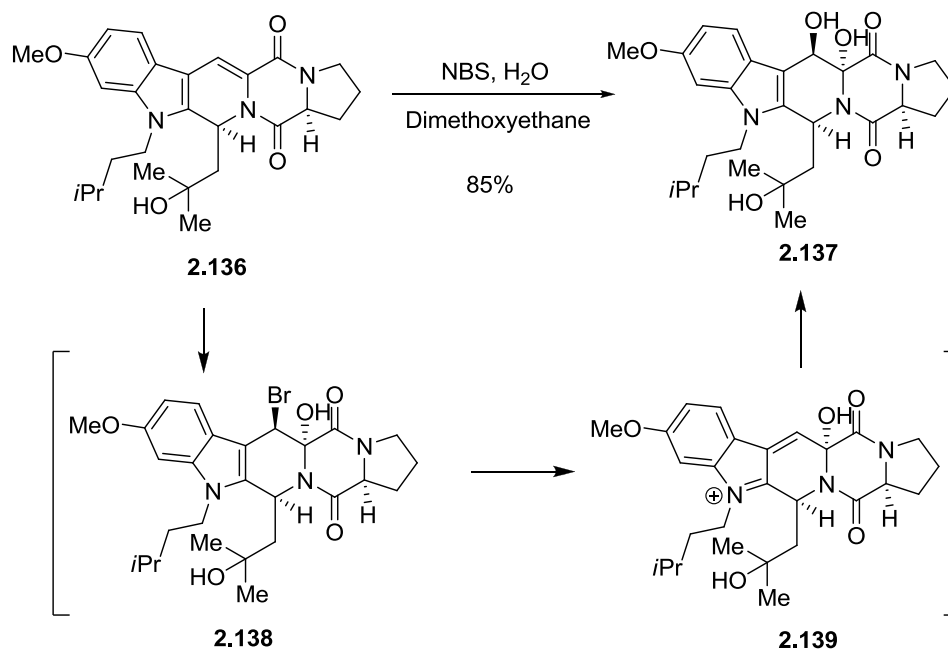
desmethoxy-verruculogen TR-2 (**2.134**) (Scheme 2.23) by Boyd.¹⁶⁰ Exposure of **2.135** to a slight excess of osmium tetroxide in pyridine, followed by reductive workup, delivered the natural product **2.134** in 75% yield as a single diastereomer. The approach of the oxidant is thought to be directed by the steric factors around the C10 and C15 carbons.

Scheme 2.23: Late-stage oxidation to give desmethoxy-verruculogen TR-2 (**2.134**)



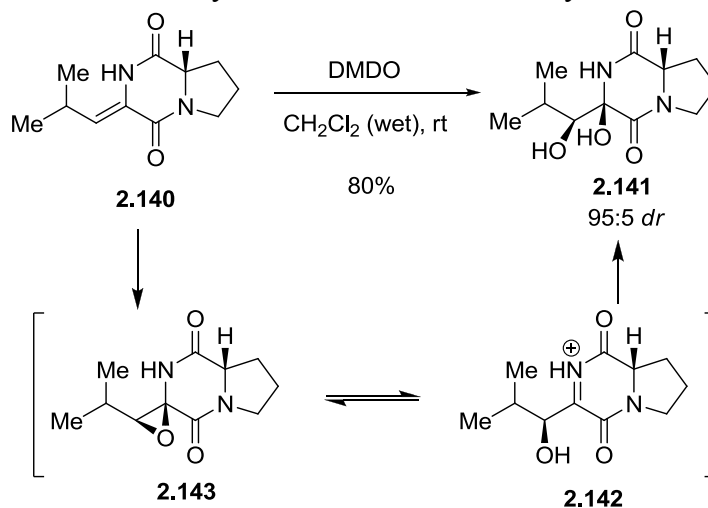
In pursuit of the closely related alkaloid (+)-fumitremorgin B, Hino and co-workers oxidized **2.136** to the *trans*-diol **2.137** using NBS and H₂O in 85% yield. (Scheme 2.24).¹⁶¹ The mechanism presumably went through the bromohydrin **2.138**, which was then converted to the diol by ionization of the bromide to give the iminium ion **2.139** that was then trapped with water.

Scheme 2.24: Oxidative conditions using NBS and water



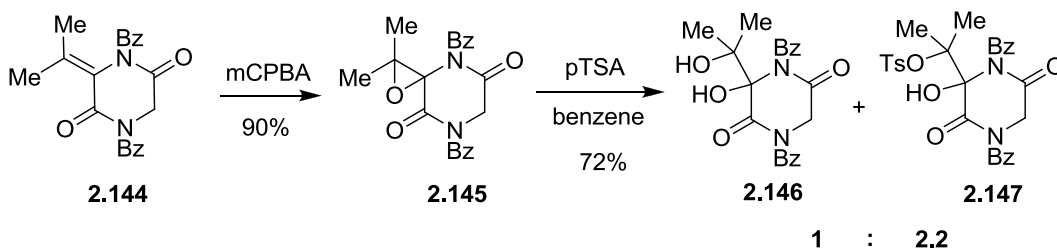
The direct oxidation of exocyclic olefins of diketopiperazines using dimethyldioxirane has been reported for the conversion of ylidene-pyrazine-2,5-dione **2.140** to diol **2.141** (Scheme 2.25).¹⁶² The methodology required the use of ‘wet’ solvent to provide water as a nucleophile to capture the iminium intermediate **2.142**, which was presumably in equilibrium with epoxide **2.143**. The reaction gave *syn*-diol **2.141** in 80% yield and 95% diastereomeric excess.

Scheme 2.25: Oxidation of exocyclic enamides with dimethyldioxirane



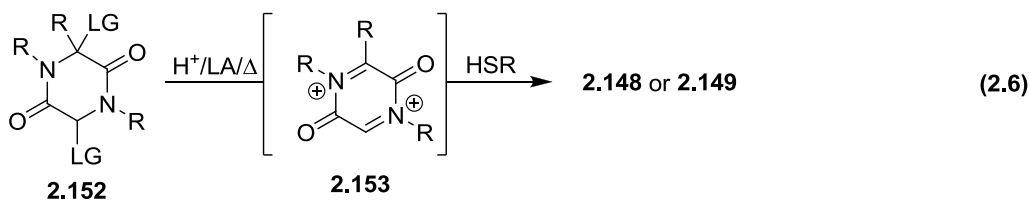
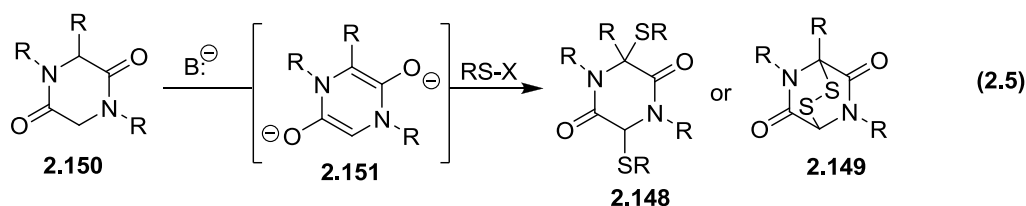
In a similar example, Yates and Hoare found that they could oxidize the tetrasubstituted exocyclic olefin of **2.144** using mCPBA, giving isolable epoxide **2.145** in 90% yield (Scheme 2.26).¹⁶³ Further elaboration of **2.145** involved ionization with toluenesulfonic acid, and trapping of the resultant cation with water, to furnish diol **2.146**, as well as tosylate **2.147**.

Scheme 2.26: Oxidation using mCPBA followed by conversion to the diol



2.2.2.5. Installation of the disulfide

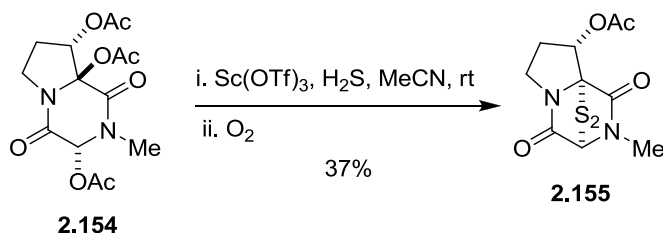
The construction of the sulfur bridge onto the diketopiperazine ring has been explored and developed in a number of seminal papers.^{164,165} Epidithiodiketopiperazines represented by **2.148** or **2.149** can generally be prepared by two general pathways. One pathway involves deprotonation of the diketopiperazines, such as **2.150**, followed by trapping the anion **2.151** (equation 2.5). A more common method features ionization of a leaving group at the α -position of the amide **2.152**, followed by nucleophilic capture of the iminium ion intermediate **2.153** by sulfur (equation 2.6).^{166,167}



This route has been used in a number of applications, including the aforementioned total syntheses of gliocladine C (**2.13**) (Scheme 2.7) and chaetocin A (**2.14**) (Scheme 2.6). A similar ionization was developed by Overman and co-workers during their study of methodology to access epidithiodiketopiperazines.¹⁶⁸ In that study, they synthesized intermediate **2.154**, which was exposed to scandium triflate and hydrogen sulfide followed by oxygen to provide the disulfide **2.155** in 37% yield (Scheme 2.27). It was suggested that the stereoselectivity of the sulfur installation was

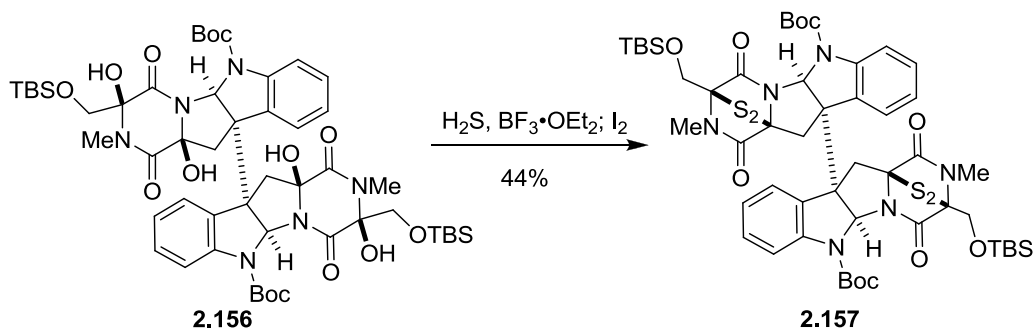
influenced by the nearby acetate functionality, which directed the hydrogen sulfide to the same face through hydrogen bonding.

Scheme 2.27: Overman's model study toward the synthesis of epidithiodiketopiperazines



The Sodeoka group utilized a similar strategy to transform tetraol **2.156** to bis-disulfide **2.157** in their total synthesis of (+)-chaetocin (**2.14**) (Scheme 2.28).¹⁶⁹

Scheme 2.28: Sulfur installation with BF_3OEt_2 and hydrogen sulfide.

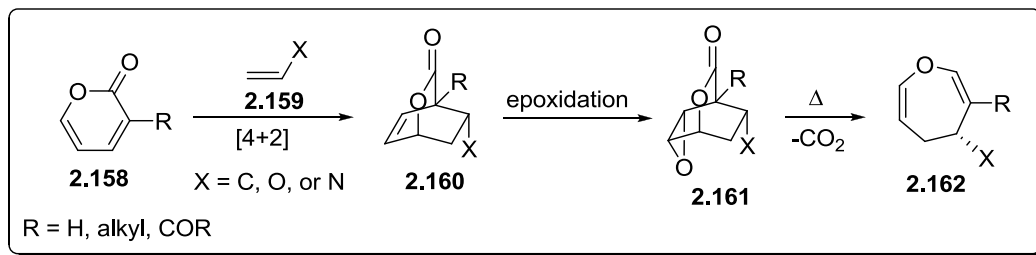


2.2.3. Proposed route to substituted oxepins by sequential pyrone cycloaddition and retro-homo Diels-Alder cycloaddition

2.2.3.1. Proposed model study

We became interested in synthetic methodology for preparing 4,5-dihydrooxepins due to our pursuit of a total synthesis of MPC1001 (**2.65**). We desired a simple procedure to generate the oxepin moiety under conditions that would not affect sensitive functionality. Upon retrosynthetic analysis of the dihydrooxepin moiety, we formulated an approach that involved a Diels-Alder cycloaddition of substituted pyrones such as **2.158** with substituted dienophiles **2.159** to give bicyclic lactones **2.160** (Scheme 2.29). This bicycle could then be epoxidized, giving **2.161** and setting up a retro-homo Diels-Alder cycloaddition to reveal the oxepin **2.162**. This model study was envisioned to demonstrate the practicality of the chemistry.

Scheme 2.29: Proposed forward synthesis of the 4,5-dihydrooxepin substructure **2.162**.

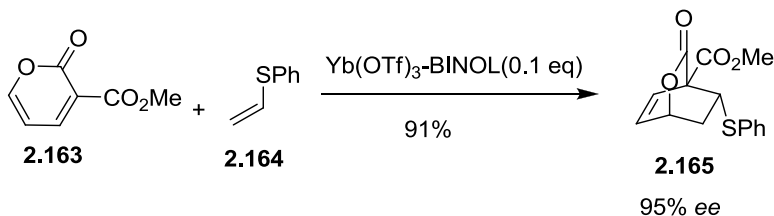


2.2.3.2. Precedent for model system

Pyrones such as **2.158** are well known to undergo inter- and intramolecular inverse electron demand Diels-Alder cycloadditions.¹⁷⁰ These [4+2] cycloadditions are generally highly regio- and diastereoselective, favoring bicyclic lactones such as **2.160** with the X-group oriented opposite of the lactone bridge and proximal to the carbonyl group. Cycloadditions of this type typically require the presence of a mild Lewis acid or high pressure to go to completion,¹⁷¹ whereas the intramolecular variant can occur spontaneously at room temperature.¹⁷²

One example is the enantioselective cycloaddition of 3-carbomethoxy pyrone (**2.163**) and phenyl vinyl sulfide (**2.164**) using Yb(OTf)₃ and (S)-BINOL to give cycloadduct **2.165** in 91% yield and 95% enantiomeric excess (Scheme 2.30).¹⁷³ This methodology was generally applicable to a wide range of vinyl ethers and sulfides.

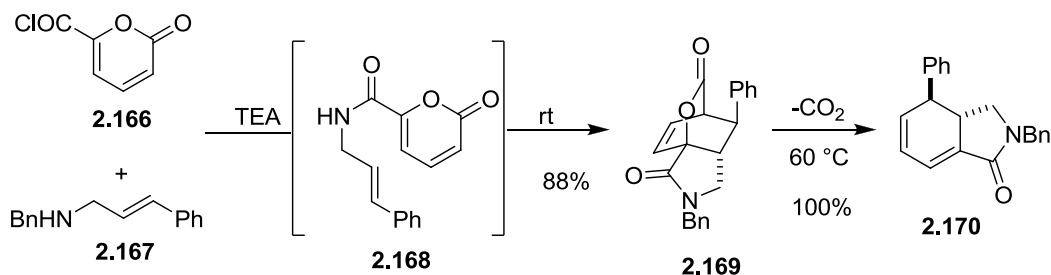
Scheme 2.30: Inverse electron demand Diels-Alder reaction with pyrones



Noguchi and co-workers reported an intramolecular pyrone Diels-Alder reaction by mixing acid chloride **2.166** and the benzylamide **2.167** in the presence of triethylamine to provide intermediate **2.168** (Scheme 2.31).¹⁷² The cyclization of **2.168** occurred rapidly at room temperature, giving tricyclic lactone **2.169** in 88% yield. Heating the

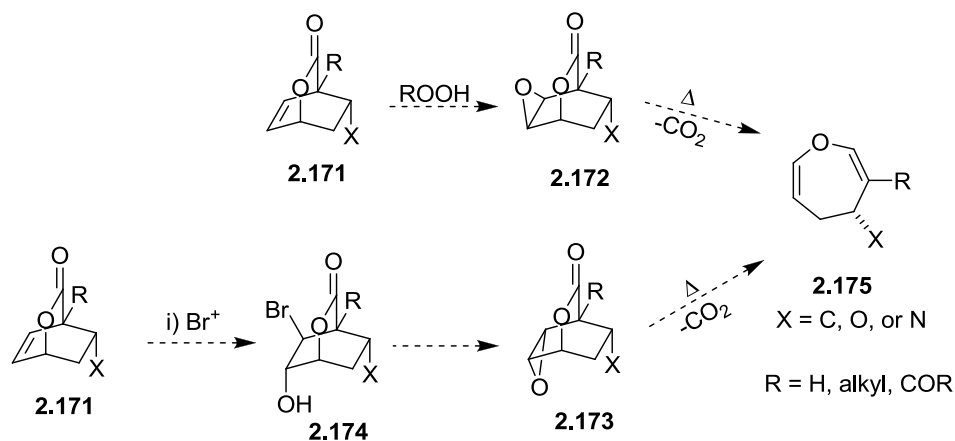
resultant cycloadduct at 60 °C quantitatively converted **2.169** to diene **2.170** by extrusion of carbon dioxide.

Scheme 2.31: Intramolecular pyrone Diels-Alder followed by loss of carbon dioxide



After the cycloaddition, our plan was to oxidize the olefin moiety in **2.171** to both *exo*-epoxide **2.172** and *endo*-epoxides **2.173** (Scheme 2.32). Several examples of the epoxidation of systems similar as **2.171** are known.^{174,175} Using traditional electrophilic oxidants the epoxidation is expected to occur proximal to the lactone bridge to give the *exo*-isomer **2.172**, as this is the less hindered face of the molecule. In order to oxidize the opposite face of bicyclic system **2.171**, we planned to form the halohydrin **2.174** followed by a base promoted ring closure of **2.173**, which is a known sequence to form epoxides on the more hindered face **2.171**.¹⁷⁶ We planned to screen both epoxides **2.172** and **2.173** under thermal conditions for conversion to substituted oxepin **2.175**. However, based on the aforementioned precedent, we expected *endo*-epoxide **2.173** to undergo the retro-homo Diels-Alder reaction more readily.¹⁴⁹

Scheme 2.32: Proposed examination of *endo* and *exo* epoxides

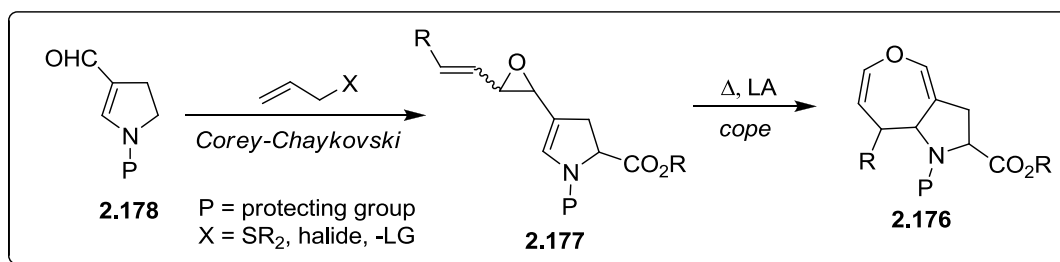


2.2.4. Route to MCP1001 core structure by Cope rearrangement of divinyl epoxide

2.2.4.1. Proposed route to MCP1001 core structure 2.176

Additionally, we proposed a concise route to access the core structure of MPC1001 **2.176** by the Cope rearrangement of a divinyl epoxide. We hoped to access the divinyl epoxide **2.177** by a Corey-Chaykovski-type epoxidation of an unsaturated aldehyde represented by **2.178** (Scheme 2.33).¹⁷⁷ The epoxidation was expected to furnish a mixture of *cis* and *trans* isomers, both of which would be evaluated, although we expected the *cis*-isomer to undergo the rearrangement to give the oxepin **2.176** under milder conditions.¹⁴⁷

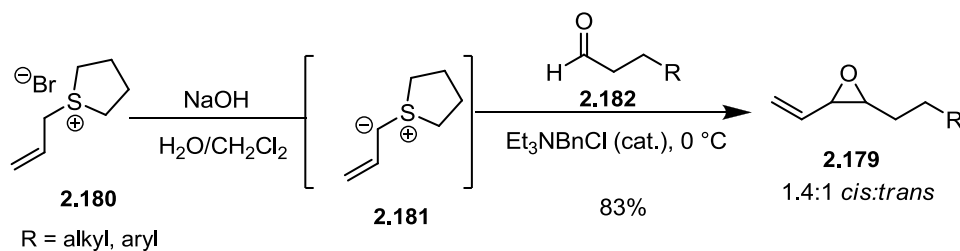
Scheme 2.33: Proposed route to substituted bicyclic oxepin cores related to MPC1001



2.2.4.2. Precedent for the conversion of 2.178 to divinyl epoxide 2.177

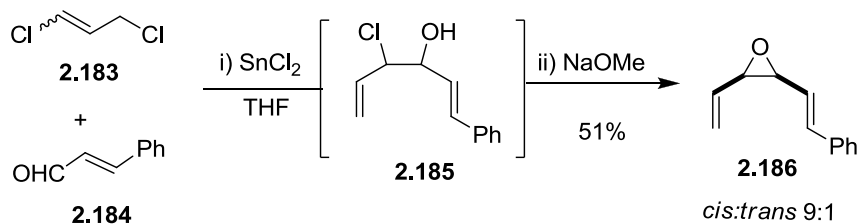
There are a number of reported conditions for the conversion of simple aldehydes to vinyl epoxides. One of the most commonly used methods was reported by Murphy and co-workers during their construction vinyl-substituted epoxide **2.179** (Scheme 2.34).¹⁷⁸ The preformed sulfonium salt **2.180** was deprotonated to form ylide intermediate **2.181**, which underwent reaction with alkyl aldehyde **2.182** giving epoxide **2.179** in 83% yield as a mixture (1.4:1) of *cis*- and *trans*-isomers. Reactions of this class have been rendered enantioselective by the use of chiral sulfur groups.¹⁷⁹ Sulfonium salts with additional substitution on the olefin have been successfully implemented.¹⁸⁰ NaOH and KOH are the most commonly used bases under biphasic conditions, although the use of K_2CO_3 , DBU and NaH has been reported under anhydrous conditions.¹⁸¹

Scheme 2.34: Epoxidation by addition of a vinyl sulfonium ylide



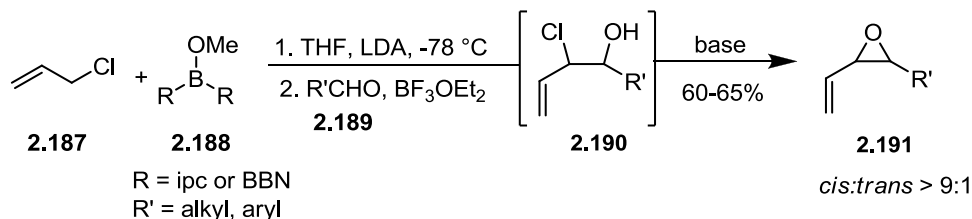
An alternative method for the formation of vinyl substituted epoxides is by the nucleophilic addition of a vinyl-metal nucleophile followed by a basic workup. In a report by Auge and Serge, dichloropropene **2.183** premixed with tin chloride was added to unsaturated aldehyde **2.184** leading to chlorohydrin **2.185** (Scheme 2.35).¹⁸² Exposure of **2.185** to sodium methoxide formed the epoxide **2.186** in 51% yield as a mixture (9:1) of *cis*- and *trans*- isomers. Similar transformations have been reported using organo-zinc,¹⁸³ chromium, palladium,¹⁸⁴ and indium metals.¹⁸⁵

Scheme 2.35: Formation of *cis*-divinyl epoxides from unsaturated aldehydes



A alternative method, which was originally pioneered by the Oehlschlager group, involves the Brown-type allylation of a vinyl-borane and an aldehyde (Scheme 2.36).¹⁸⁶ A vinyl borane species was generated by the deprotonation of allyl chloride (**2.187**) with LDA and methoxy boronate **2.188** and when aldehyde **2.189** was added the chlorohydrin **2.190** was formed. The intermediate can then be cyclized with base to give vinyl substituted epoxides **2.191** in 60-65% yield and excellent selectivity for the *cis*-isomer (>9:1). The method can be rendered enantioselective by the use of chiral boronates (R= isopinocampheyl), leading to epoxides **2.191** in as high as 98% enantiomeric excess. This methodology has been used in several total syntheses of complex natural products.^{187,188}

Scheme 2.36: Brown-type allylation of aldehydes to generate chlorohydrins



To our knowledge, Corey-Chaykovsky type transformations have never been reported with an unsaturated aldehyde such as **2.178**. We hope to adapt one of the aforementioned methodologies to such a system, seeing as there is precedent for nucleophilic additions to similar vinylogous systems.^{189,190} There is not, however, precedent for the addition of allyl anions such as those depicted in Schemes 2.34-2.36.

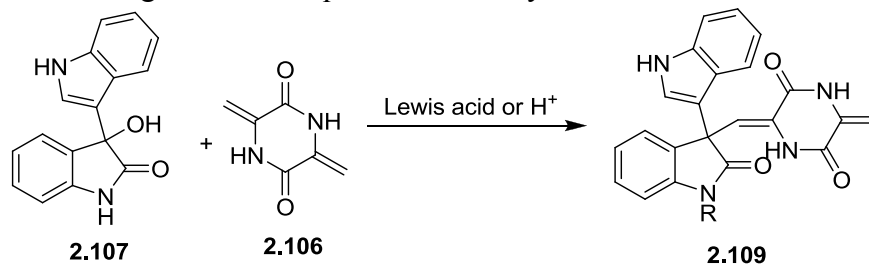
2.3. MARTIN GROUP SYNTHETIC EFFORTS TO DIKETOPIPERAZINE CONTAINING ALKALOIDS

2.3.1. Synthetic efforts toward the synthesis of hexahydropyrroloindoline alkaloids

2.3.1.1. Exploration of the cation capture using diketopiperazine **2.106** as a nucleophile

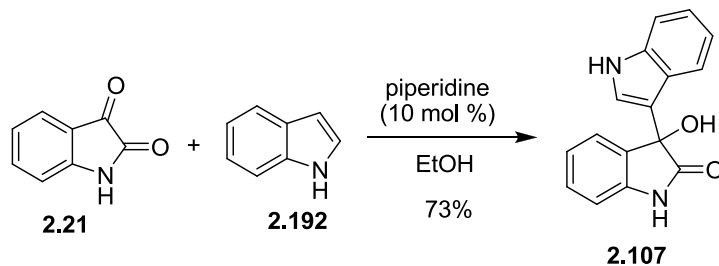
Initial synthetic efforts were focused on the synthesis of the 3,3-disubstituted oxindole **2.109**. We envisioned this intermediate could arise by a coupling of 3-hydroxy oxindole **2.107** with the diketopiperazine **2.106** (Scheme 2.37), so we sought an efficient method to prepare both starting materials.

Scheme 2.37: Starting materials required for the key bond construction



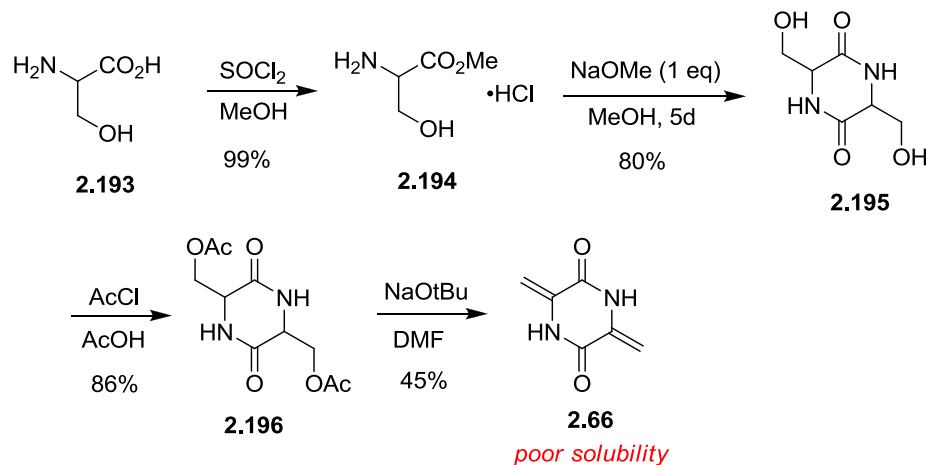
Following a known procedure, isatin (**2.21**) and indole (**2.192**) were mixed in the presence of a catalytic amount of piperidine to provide the oxindole **2.107** in 73% yield after crystallization (Scheme 2.38). This procedure allows for the facile synthesis of large amounts of **2.107**, but because **2.107** discolors upon prolonged exposure to light it should be stored in darkness.

Scheme 2.38: Piperidine catalyzed synthesis of 3-hydroxy oxoindole **2.107**.



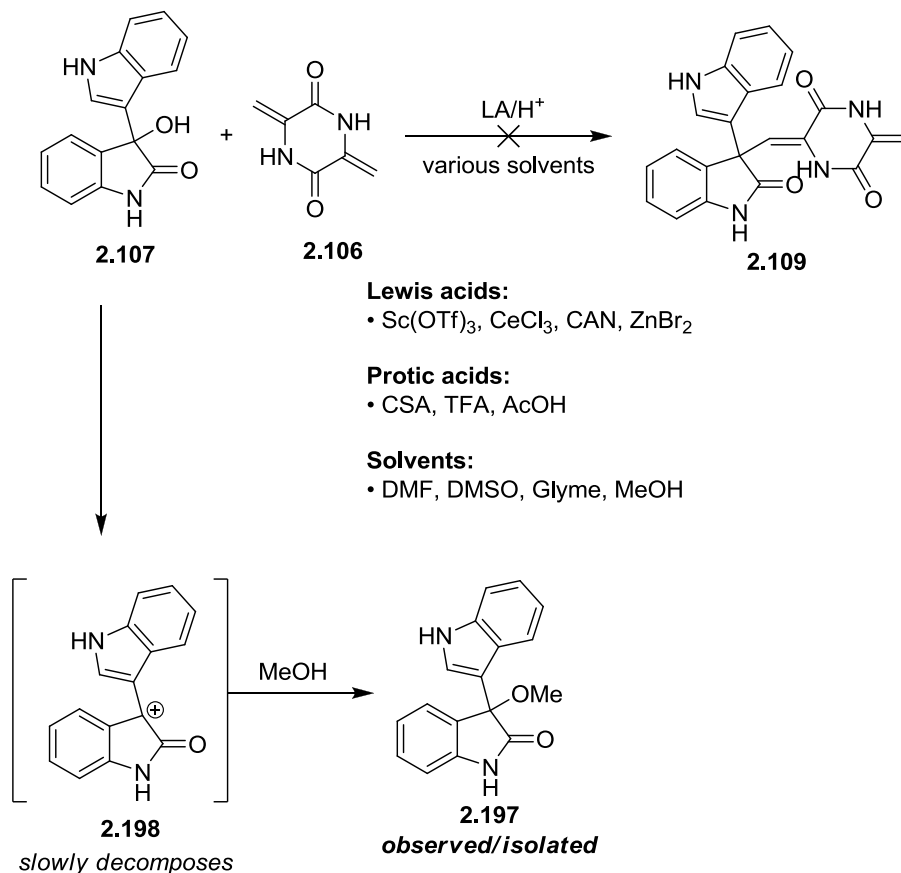
In order to prepare the bis-unsaturated diketopiperazine **2.106**, we first converted serine (**2.193**) to **2.194** with methanol and thionyl chloride (Scheme 2.39). The free-base slowly dimerized to form the diketopiperazine **2.195** in 80% yield according to a known literature procedure.¹⁹¹ The diol was then acylated using a known protocol by dissolving **2.195** in hot acetic acid followed by the dropwise addition of acetyl chloride to give¹⁹² the bis-acetylated product **2.196** in 86% yield. The acyl groups were envisioned to act as leaving groups for elimination under basic conditions. After screening a number of alkoxide and amine bases, it was found that sodium *tert*-butoxide in DMF effected the elimination, giving complete conversion of **2.196** into **2.106**. Despite the excellent conversion, we isolated dihydro diketopiperazine **2.106** in only 45%, despite efforts to optimize the reaction. The low yield of **2.106** is most likely due to its poor solubility in organic solvents, which made workup and isolation problematic.

Scheme 2.39: Dimerization of serine and elimination to access nucleophile **2.106**



With starting materials **2.106** and **2.107** in hand, we set out to test the key bond formation to give 3,3-disubstituted oxindole **2.109** (Scheme 2.40). Our strategy was to mix the starting materials together and expose them to a variety of Lewis acids [$\text{Sc}(\text{OTf})_3$, CeCl_3 , cerium ammonium nitrate, and ZnBr_2] and protic acids (CSA, TFA, AcOH). The poor solubility of **2.106** was a constant problem, limiting our solvent choice to DMF, DMSO, glyme, or MeOH. A variety of conditions were screened with multiple combinations of Lewis and protic acids, solvents, temperatures, concentrations, and reaction times, but we failed to isolate any trace of the desired product **2.109**.

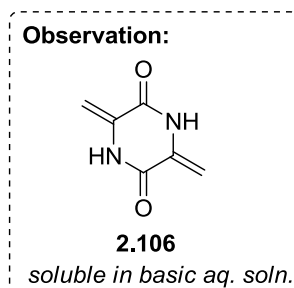
Scheme 2.40: Initial failed attempts to form disubstituted oxindole **2.109**



When the reaction was run in non-nucleophilic solvents, bis-enamide **2.106** was recovered unchanged; however, hydroxyoxindole **2.107** slowly decomposed to an intractable mixture of products. When the reaction was run in methanol, we observed no reaction involving **2.106**; however, we did observe the quantitative conversion of alcohol **2.107** to **2.197**. No polymerization was detected under these conditions. This is evidence that we are indeed ionizing **2.107**, but diketopiperazine does not appear to react as a nucleophile with **2.198**. During experimentation we observed that the solubility of diketopiperazine **2.66** in aqueous solutions was pH dependent, exhibiting better solubility

in alkaline solutions (Figure 2.6). This led us to believe that the enamide protons are quite acidic, and that, deprotonation might lead to a more reactive nucleophile.

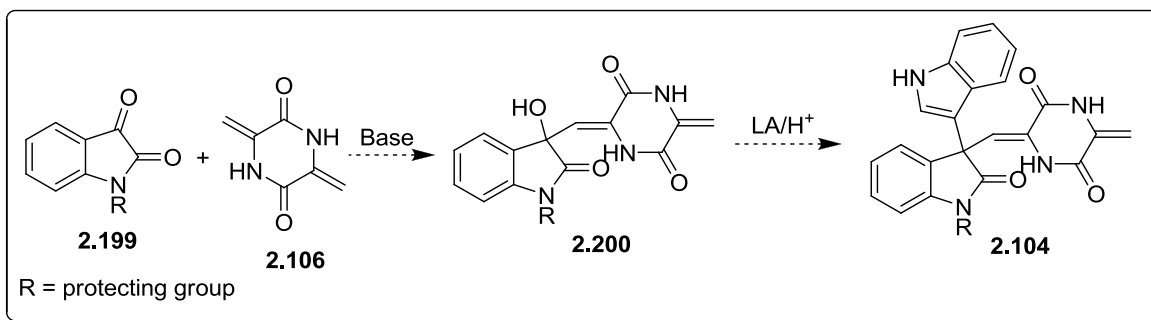
Figure 2.6: Observations during the course of the condition screening



2.3.1.2. Re-worked forward synthesis of 2.104 using base promoted nucleophilic addition

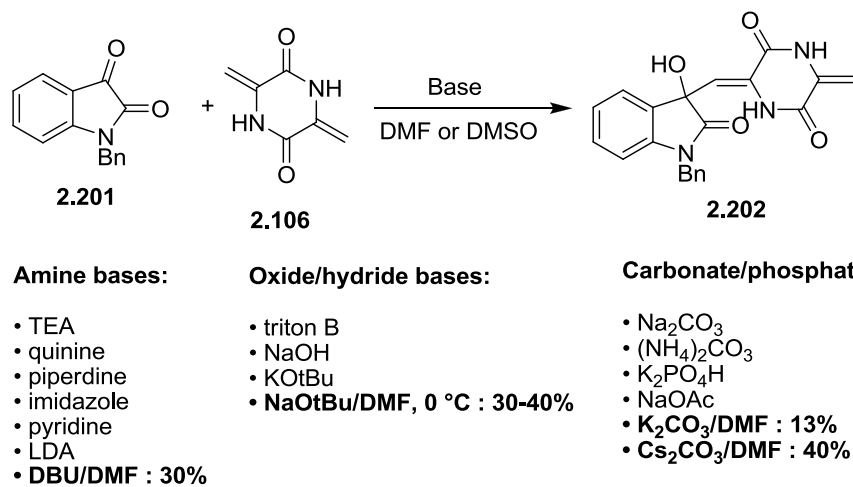
When considering the use of **2.106** as a nucleophile under basic conditions, we encountered a potential problem with our approach: we required acidic conditions to ionize the tertiary alcohol of **2.107** but basic conditions may be needed to activate **2.106** as a nucleophile. This analysis led to a revision of our synthetic approach (Scheme 2.41). We thus envisioned a resequencing of the steps, wherein protected isatin **2.199** would first react with **2.106** under basic conditions to give the intermediate allylic alcohol **2.200** that would undergo ionization in the presence of a Lewis acid and indole to give our key disubstituted oxoindole **2.104**.

Scheme 2.41: Reworked forward synthesis of **2.104**



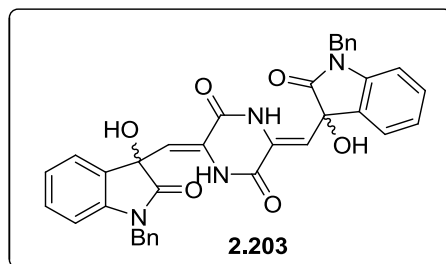
To explore the feasibility of this new route, *N*-benzyl protected isatin **2.201** and bis-enamide **2.106** were dissolved in DMF or DMSO and exposed to a variety of bases, temperatures, times, and concentrations (Scheme 2.42). The isatin was protected to avoid competitive deprotonation from the amide proton. A variety of amine bases were screened, and we eventually discovered that exposure of **2.106** gave **2.202** in 30% yield. Similarly, oxide and hydride bases were screened, with NaOtBu in DMF giving **1.202** in 30-40% yield. Carbonate bases K₂CO₃ and Cs₂CO₃ in DMF also lead to **2.202** in 13% and 40% yields respectively.

Scheme 2.42: Base screening to access 3-hydroxyoxoindole **2.202**



The low yield during each of the base promoted nucleophilic additions was attributed to formation of the major side product **2.203** (Figure 2.7). We attribute this side product to the over-reaction of the initially formed product **2.202** with a second molecule of isatin **2.201**. The bis-alkylated substrate **2.203** was isolated as a mixture (1:1) of diastereomers. While this problematic side-reaction was disappointing, it did produce enough of mono-alkylated product **2.202** to allow us to test the ionization/indole addition step.

Figure 2.7: Major side product during the base-promoted nucleophilic addition



Using a small amount of 3-hydroxyindole **2.202**, we screened two ionization conditions in the presence of indole to access the 3,3-disubstituted oxindole **2.204**. Unfortunately, exposure of **2.202** to scandium triflate or camphorsulfonic acid failed to produce any of the desired addition product **2.204** (Scheme 2.43). Both reactions did, however, produce **2.205** in 30-55% yield as a mixture (1.6:1.0) of diastereomers. A single isomer **2.206** was isolated from this mixture and its structure was determined by X-ray crystallography (Figure 2.8). Despite not isolating any of the desired product, the synthesis of hydroxyoxindole **2.202** and side product **2.205** were critical results that served as a proof-of-principal for future improvement.

Scheme 2.43: Attempted ionization and indole trapping.

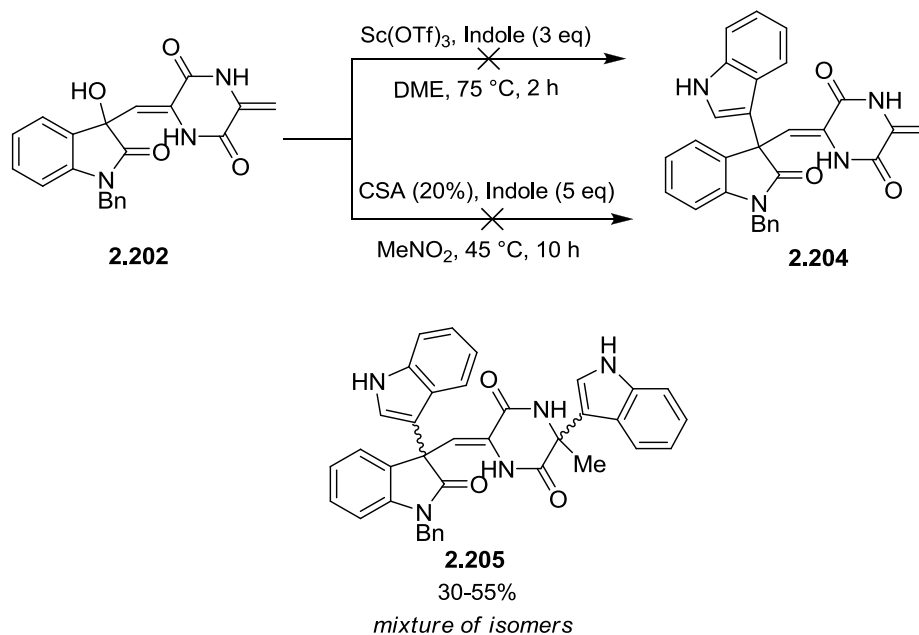
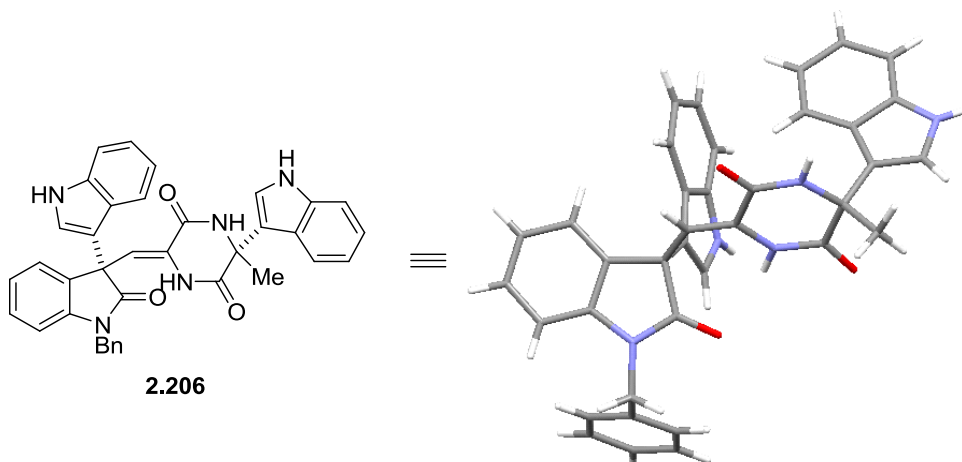


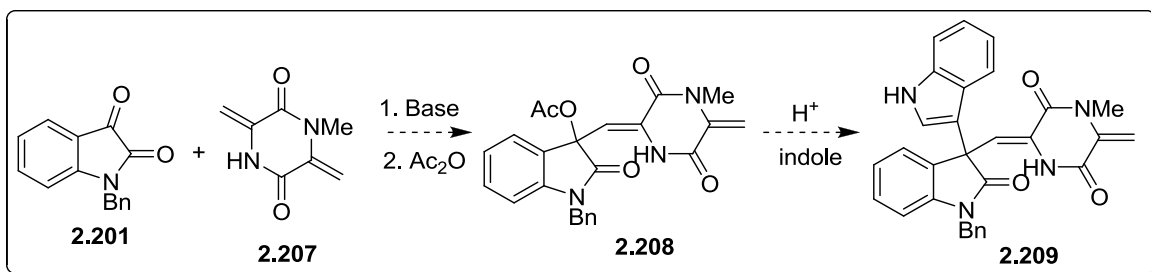
Figure 2.8: Isolation and structure determination of side product **2.206**



2.3.1.3. 2nd generation synthesis of 2.209 by base induced nucleophilic attack

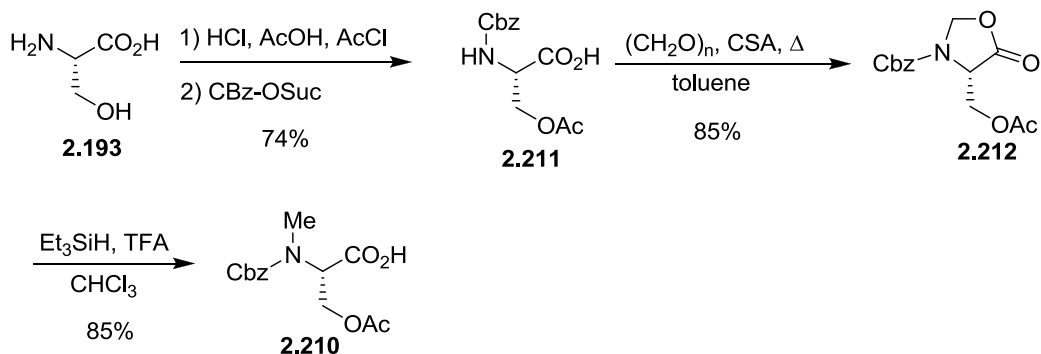
In light of these problems, we redesigned the route in order to avoid over-reaction during the ionization/indole trapping sequence and to improve the yields of the nucleophilic diketopiperazine addition (Scheme 2.44). By replacing symmetrical diketopiperazine **2.106** with mono-methyl nucleophile **2.207** we felt that we could avoid the formation of the double addition products such as **2.203** because only one of the enamides would be nucleophilic under basic conditions. Furthermore, we hoped that by activating the resultant tertiary alcohol by transformation to acetate **2.208**, we could synthesize oxoindole **2.209**. The reasoning for this hypothesis is that under acidic conditions the tertiary acetate **2.208** would be a much better leaving group, thus it would ionize selectively before external enamide, thus avoiding the formation of side products such as **2.205**.

Scheme 2.44: Redesigned route using mono-methyl diketopiperazine nucleophile **2.132**



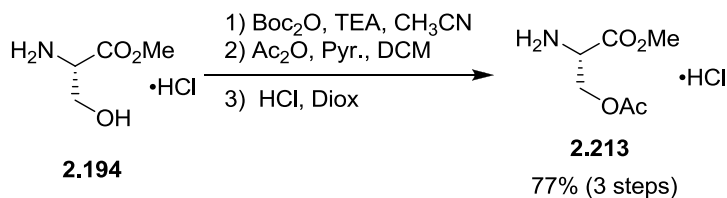
An early challenge in the development of this second generation route was the synthesis of unsymmetrical diketopiperazine **2.207**. Common strategies for the synthesis of unsymmetrical heterocycles such as **2.207** require that the individual amino acids be prepared separately, coupled, and cyclized.^{193,194} Accordingly, we prepared *N*-methyl amino acid **2.210**. Following an approach first developed by Hughes and co-workers,¹⁹⁵ the free hydroxyl group of serine (**2.193**) was first protected using acetyl chloride under acidic conditions (Scheme 2.45). This *O*-acetylated amino acid was then *N*-protected with *N*-(benzyloxycarbonyloxy)succinimide to give bis-protected serine derivative **2.211** in 74% yield over the two steps. Exposure of **2.211** to paraformaldehyde and catalytic camphor sulfonic acid gave cyclic oxazolidinone **2.212** in 85% yield. Reductive cleavage of **2.212** using trifluoroacetic acid and triethylsilane, gave **2.210** in 85% yield. This sequence requires no chromatography and allowed us efficiently produce considerable quantities of **2.210**.

Scheme 2.45: Synthesis of *N*-methyl serine derivative **2.210**.



The other half of **2.207** originated from acetylated serine methyl ester hydrochloride salt **2.194** (Scheme 2.46). The synthesis of **2.213** was accomplished in by *N*-Boc protection of **2.194** using Boc-anhydride and triethylamine followed by hydroxyl protection with acetic anhydride. Formation of the HCl salt with concomitant deprotection of the *N*-Boc group gave **2.213** in 77% overall yield.

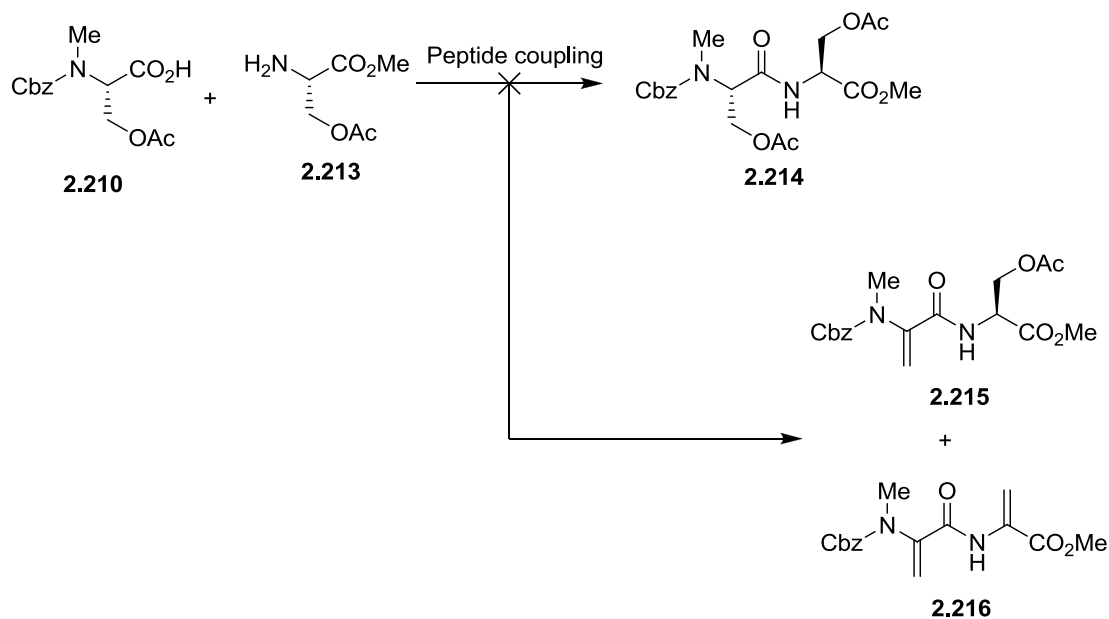
Scheme 2.46: Three step synthesis of acetyl-serine methyl ester **2.213**.



The coupling of **2.210** and **2.213** was then explored. Disappointingly, all attempts to couple the peptides under a variety of common conditions failed to give dipeptide **2.214** in appreciable yield. The reactions consistently gave mixtures of multiple products, primarily unsaturated dipeptides **2.215** and **2.216** (Scheme 2.47). The problem

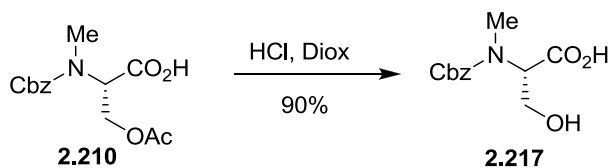
appears to be associated with the labile acetate groups, which are prone to elimination even under mildly basic conditions. The route was then redesigned to avoid this problem.

Scheme 2.47: Failed coupling of **2.210** and **2.213** due to labile acetates



Exposure of **2.210** to HCl in dioxane cleanly produced the deprotected serine derivative **2.217** in 90% yield (Scheme 2.48).¹⁹⁵

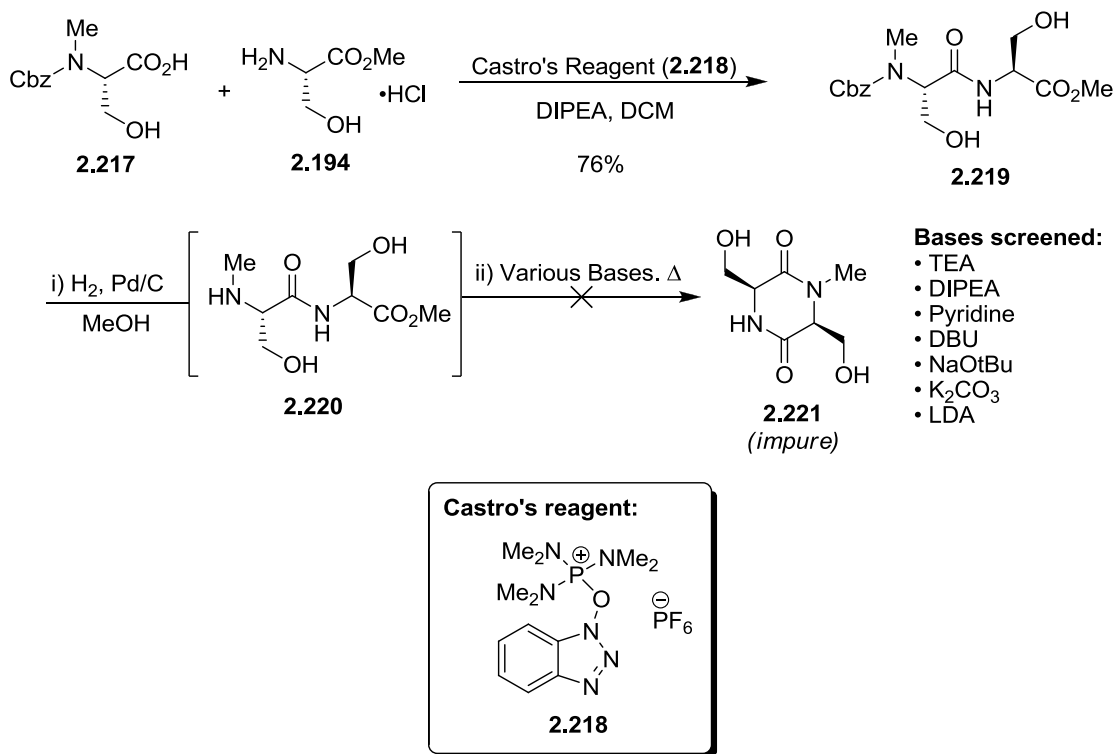
Scheme 2.48: Synthesis of *N*-Methyl-*N*-Cbz-serine **2.217** from **2.210**.



The coupling of peptides **2.217** and **2.194** proceeded without event on large scale using commercially available Castro's reagent (**2.218**) and diisopropylethylamine to furnish dipeptide **2.219** in 76% yield after flash chromatography on silica gel (Scheme 2.49). This represents the first time that chromatography was used in the route. Other coupling reagents were not evaluated due to our desire to test the downstream chemistry.

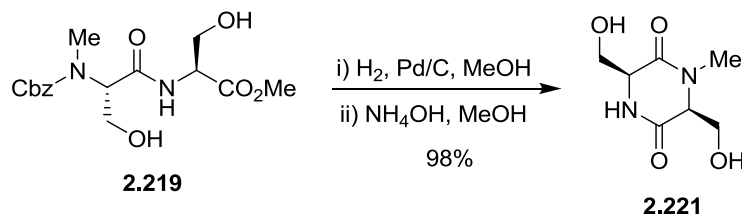
The cyclization of **2.219** to diketopiperazine **2.221** was initially problematic. The *N*-deprotection proceeded cleanly under standard conditions using palladium on carbon under an atmosphere of hydrogen to give **2.220**, together with desired product **2.221**. Because **2.220** and **2.221** are only soluble in highly polar solvents such as DMF, MeOH, and DMSO purification was a problem. In order to avoid the need for a chromatographic purification procedure, we required cyclization conditions that cleanly gave **2.221**. We screened numerous basic conditions, including the use of amines, alkoxides, and amide bases. While many of these conditions gave significant amounts of desired heterocycle **2.221**, this product was invariably contaminated with polypeptide side products or starting dipeptide **2.220**.

Scheme 2.49: Coupling of peptides **2.217** and **2.194**, and failed cyclization conditions



We eventually found that we could limit side reactions and get full conversion of **2.219** to **2.221** by running the cyclization in the presence of 7.5 wt% ammonium hydroxide (37% $\text{NH}_3/\text{H}_2\text{O}$) in dilute methanol to give **2.221** in 98% yield (Scheme 2.50).¹⁹⁶ The formation of a single product and complete consumption of starting material allowed us to simply filter and concentrate the solution, rendering solid **2.221** that required no further purification

Scheme 2.50: Successful deprotection and cyclization sequence



The next step required the elaboration of diketopiperazine **2.221** into bis-unsaturated nucleophile **2.207**, but the poor solubility of **2.221** was problematic. We found that we could improve the solubility of **2.221** and activate the alcohols toward elimination by first silylating the hydroxyl groups with TBSCl in DMF (Scheme 2.51). Exposure of the crude product to sodium *t*-butoxide afforded the bis-enamide **2.207** in 35% yield over two steps. We suspected that the low yield can be attributed to the poor solubility profile of bis-unsaturated diketopiperazine **2.207**, which made isolation difficult. Despite the difficulties in preparing and handling **2.207**, we were able to access small quantities of pure **2.207** for screening in the next step. When a solution of **2.207** and isatin **2.201** in DMF was treated with anhydrous potassium carbonate, 3-hydroxyoxindole **2.202** was isolated in 34% yield as a single *cis/trans* isomer. The difficulties associated with the handling of **2.207** prompted us to explore the possibility of developing a modified procedure that would avoid isolation of intermediate **2.207** thereby increasing the overall yield of **2.202**. After some experimentation, we found that the alcohols of **2.221** could be activated with mesyl chloride in DMF and eliminated with triethylamine a single synthetic operation. Once all starting materials were converted to bis-unsaturated nucleophile **2.207**, *N*-benzylisatin (**2.201**) and potassium carbonate were added to the reaction mixture in a single portion. Gratifyingly, after stirring at room

temperature for two days, the reaction was worked up, giving the desired product **2.202** was obtained in 71% yield from **2.221** after chromatography. The structure of **2.202** was confirmed by X-ray crystallography (Figure 2.9). This streamlined procedure allowed us to access preparative amounts of hydroxyindole **2.202**.

Scheme 2.51: Development of one-pot activation, elimination, isatin addition procedure

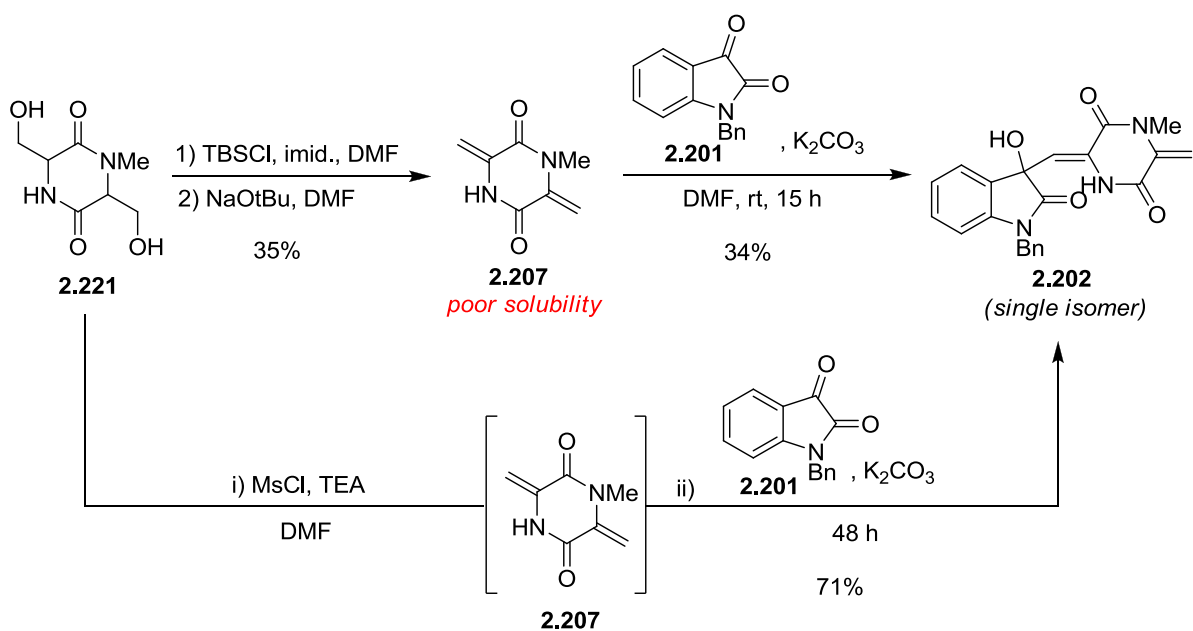
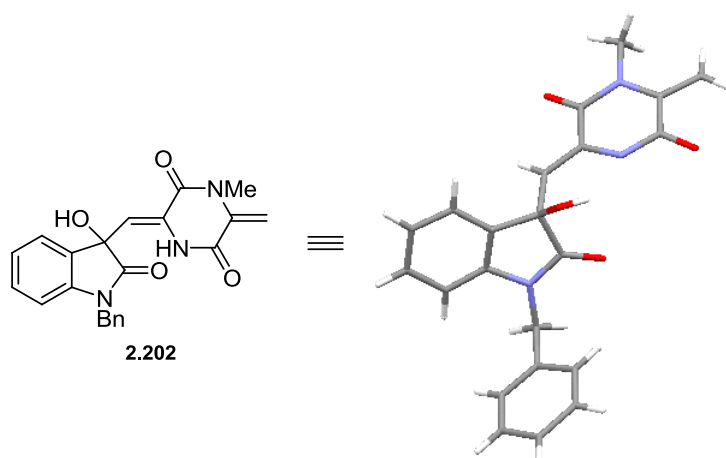
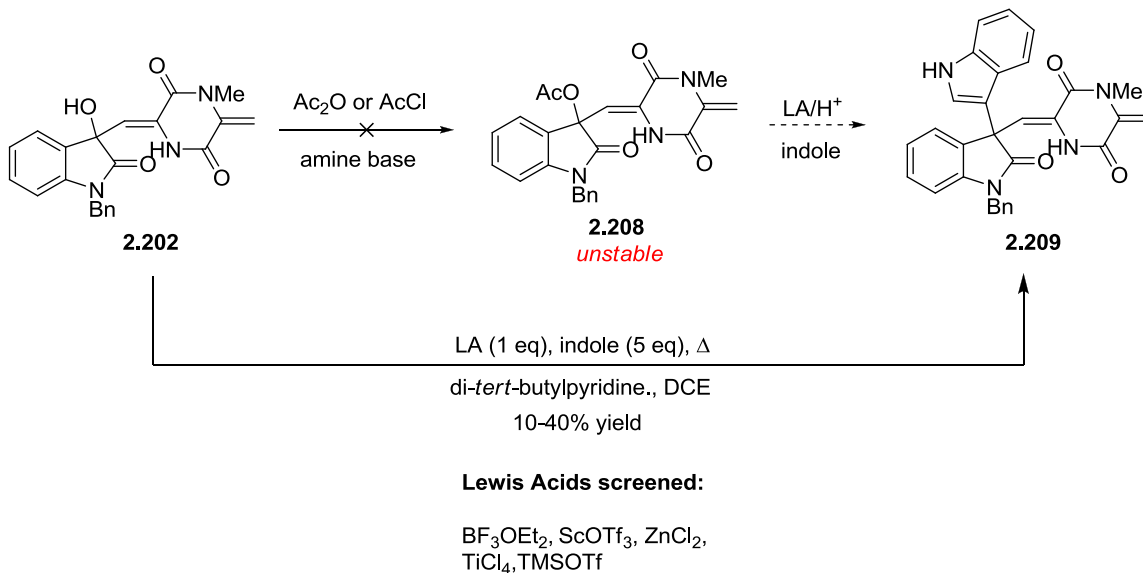


Figure 2.9: X-ray crystal structure of **2.202**



With significant quantities of **2.202** in hand, we set out to explore conditions to activate the tertiary alcohol of **2.202**. After some initial experiments, it became apparent that the product formed by acetylation of **2.202** was unstable, and we were never able to characterize **2.208** (Scheme 2.52). We then explored a one-pot synthesis of **2.209** without first derivatizing the alcohol **2.202**. When **2.202** was treated with various Lewis acids in the presence of indole and di-*tert*-butyl-pyridine (**1.182**), the 3,3-disubstituted oxindole **2.209** was obtained in 10-40% yield. From these experiments, we determined that the best promoters for this reaction were BF₃OEt₂ and TMSOTf.

Scheme 2.52: Ionization and indole trapping to access 3,3-disubstituted oxoindole **2.209**



Optimization of the reaction sequence led to identifying the conditions shown in Scheme 2.53. By increasing the amount of TMSOTf to two equivalents, we were able to lower the reaction temperature from 100 °C to 75 °C and increase the yield of **2.209** to 80%. The structure of **2.209** was confirmed by X-ray crystallography (Figure 2.10).

Scheme 2.53 Improved conversion of **2.202** to **2.209** using TMSOTf.

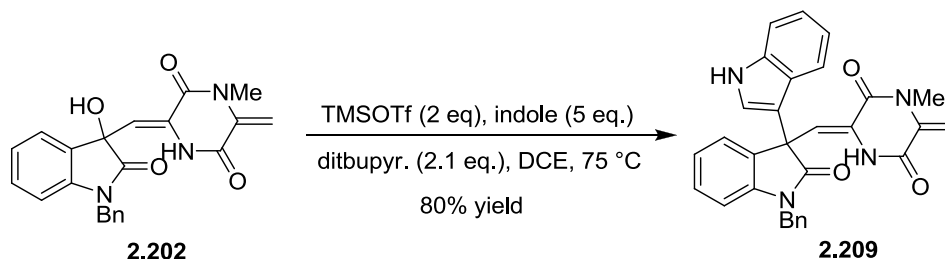
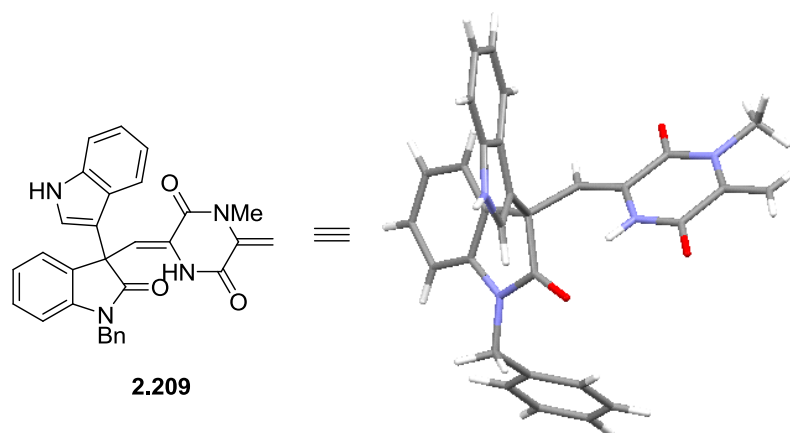


Figure 2.10 Structure confirmation of **2.209** with X-ray crystallography

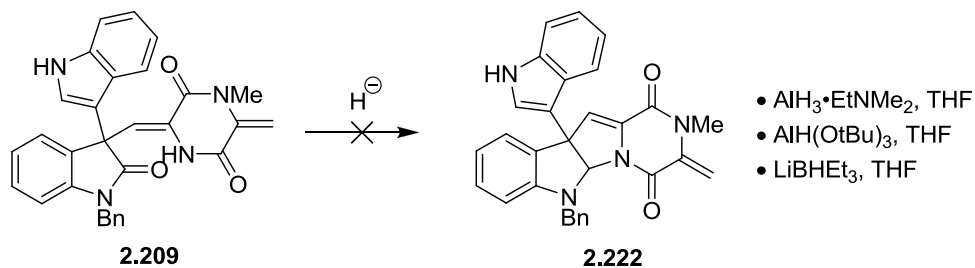


2.3.1.4. Development of the reductive ring-closure of 2.209

In order to access the core hexacyclic structure, we sought to develop conditions for the reductive ring closure of **2.209** to **2.222**. While we were aware of precedent for this type of reaction, there were some major concerns.¹⁵⁵ Oxindole **2.209** and amination **2.222** contain a number of reducible functional groups that increase the possibility for side reactions. Besides the carbonyl group of the oxindole, there is the possibility of reducing the carbonyl groups of the diketopiperazine ring, as well as the potential for 1,4-reduction of the enamide functions.

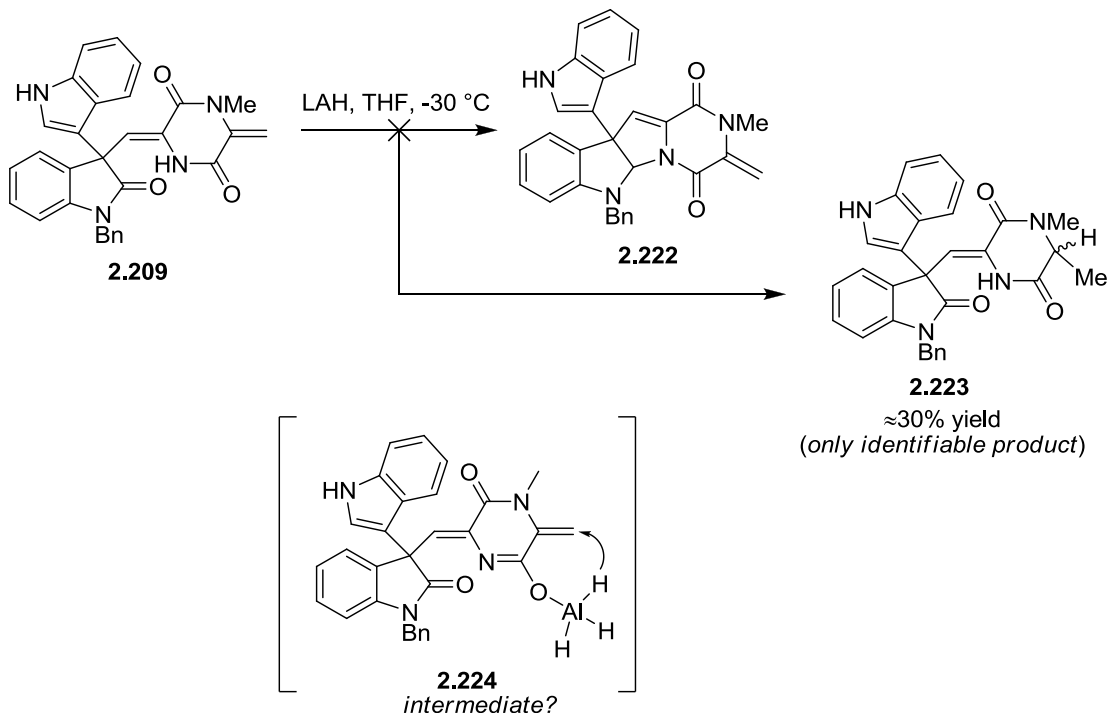
In initial experiments, we examined the use of $\text{AlH}_3 \cdot \text{NEtMe}_2$, $\text{AlH}(\text{O}t\text{Bu})_3$, and LiBHET_3 . Discouragingly, when **2.209** was exposed to these reducing agents at $-50\text{ }^\circ\text{C}$, the starting material decomposed into a complex mixture of products (Scheme 2.54). In the reaction of alane-dimethylethylamine complex with **2.209**, we detected trace amounts of **2.222** by LCMS; however, **2.222** was never isolated from the reaction mixture.

Scheme 2.54: Failed reductive coupling of **2.209** with common reducing agents



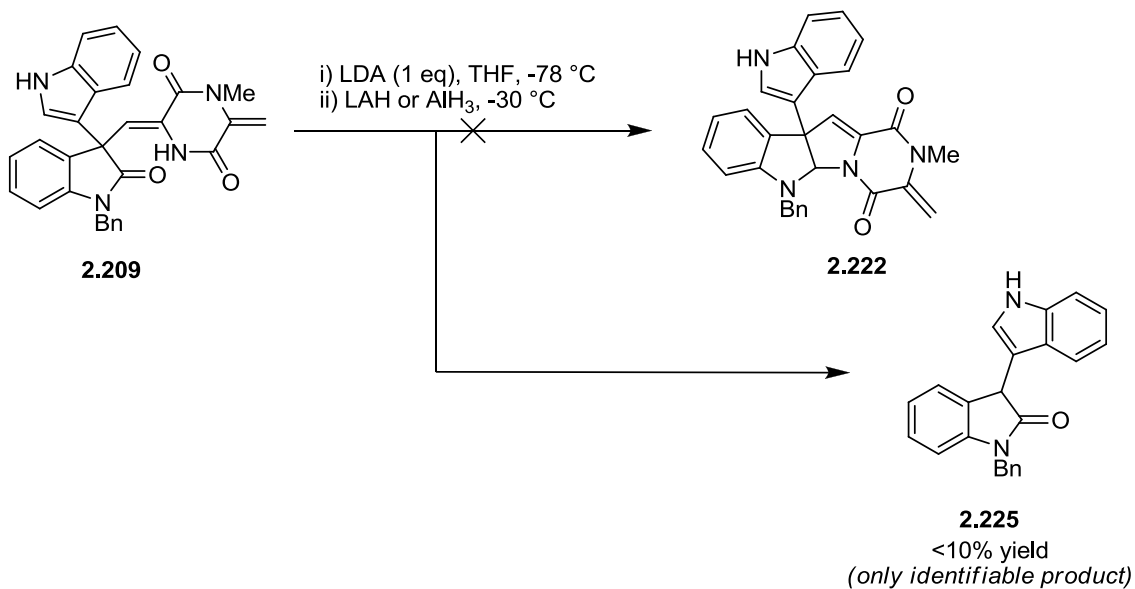
Attempts to use lithium aluminum hydride for the reductive cyclization of **2.209** were also not successful. When **2.209** was exposed to lithium aluminum hydride at cold temperatures in THF, no trace of **2.222** was detected (Scheme 2.55). Instead, we observed the rapid formation of a complex mixture of products. The major product was the methyl substituted diketopiperazine **2.223** which was isolated in near 30% yield. We suspected that this product arose by the deprotonation of the free enamide of **2.209** to give the coordinated aluminum hydride **2.224**, which then undergoes hydride addition *via* a 6-membered transition-state to reduce the external olefin.

Scheme 2.55: 1,4-Reduction of the external olefin using lithium aluminum hydride



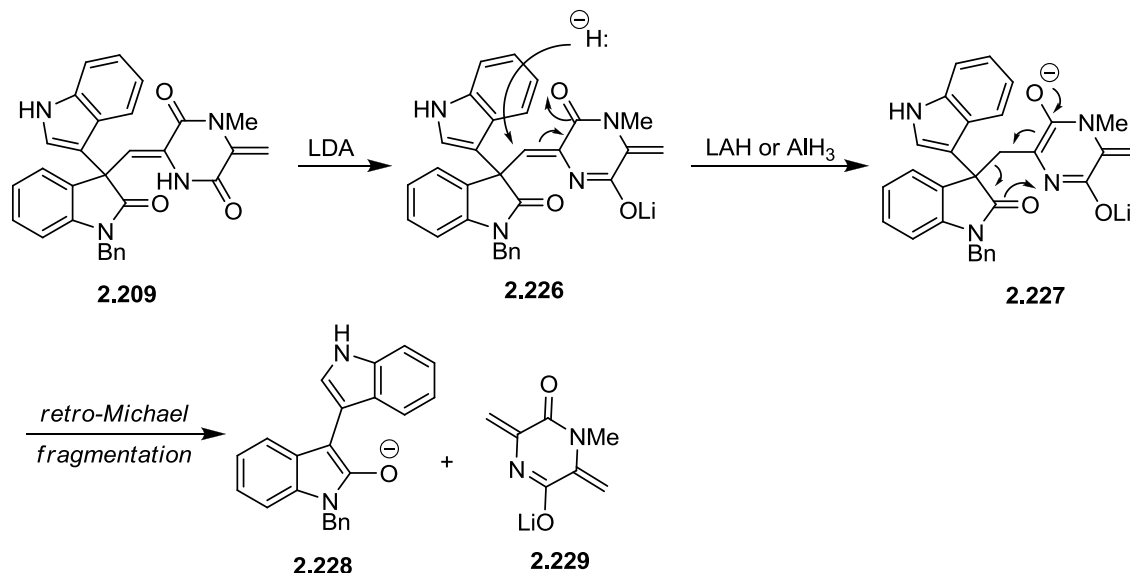
In order to circumvent this deleterious side reaction, we sought to deactivate the free enamide of **2.209** by deprotonation prior to exposure to the reducing agent. To this end, we first treated **2.209** with one equivalent of freshly prepared lithium diisopropylamide in THF at $-78\text{ }^{\circ}\text{C}$ prior to the addition of either lithium aluminum hydride or alane-*N,N*-dimethylethylamine complex at $-30\text{ }^{\circ}\text{C}$ (Scheme 2.56). In both cases, we failed to detect any trace of the desired product **2.222**, and we consistently observed the formation of the fragmentation product **2.225** in as much as 10% yield. No other products could be isolated or identified from the reaction mixture.

Scheme 2.56: Deprotonation of **2.209** with LDA prior to addition of hydride sources



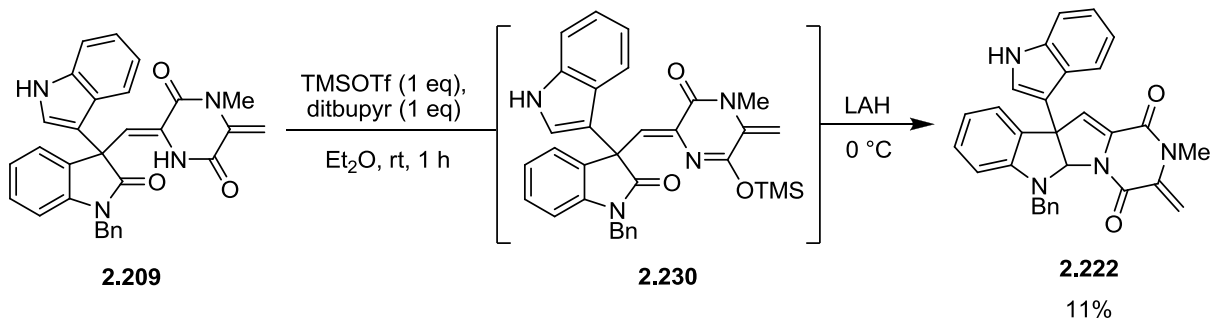
We suspected that **2.225** arises *via* the mechanistic pathway shown in Scheme 2.48. Disubstituted oxoindole **2.209** was first deprotonated to give the anion **2.226**. Upon addition of hydride, the internal olefin of **2.226** was reduced by 1,4-addition, leading to an unstable dianion **2.227** that collapses by a retro-Michael addition to generate anions **2.228** and **2.229**.

Scheme 2.48: Possible mechanistic explanation for the fragmentation of **2.209**.



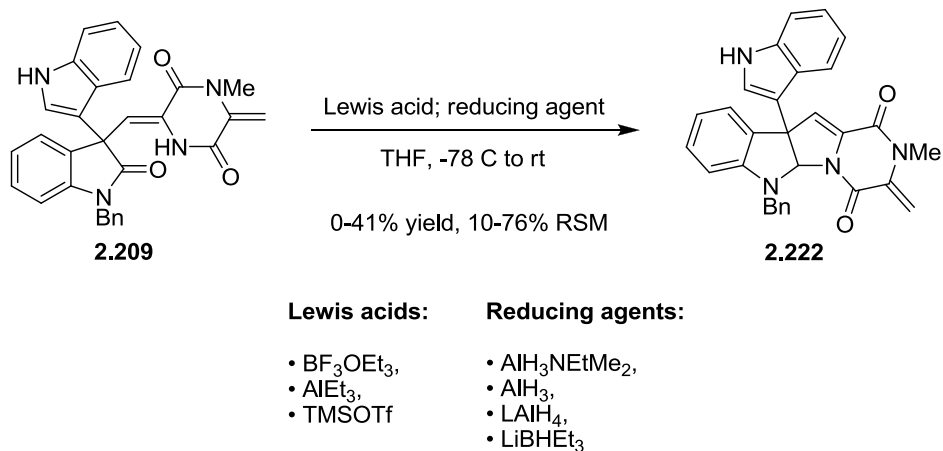
We envisioned an alternative approach in which the free enamide of **2.209** might first be protected as an intermediate such as **2.230** *in situ* prior to the reduction, thus deactivating that portion of the molecule (Scheme 2.57). To test this theory, oxindole **2.209** was exposed to TMSOTf in the presence of di-*tert*-butylpyridine. The reaction mixture was cooled to 0 °C, and lithium aluminum hydride was added. While the reaction generated a complex mixture of products, we were for the first time able to isolate and identify the desired cyclized product **2.222** in 11% yield. Questions persisted regarding how the TMSOTf was enabling the synthesis of **2.222**. Namely, was the reaction indeed proceeding *via* intermediate **2.230**, or was the effect due to the coordination of a Lewis acid to the oxindole, allowing for a more selective reduction by activation of the desired ketone?

Scheme 2.57: First successful reductive coupling of **2.209** to give core structure **2.222**



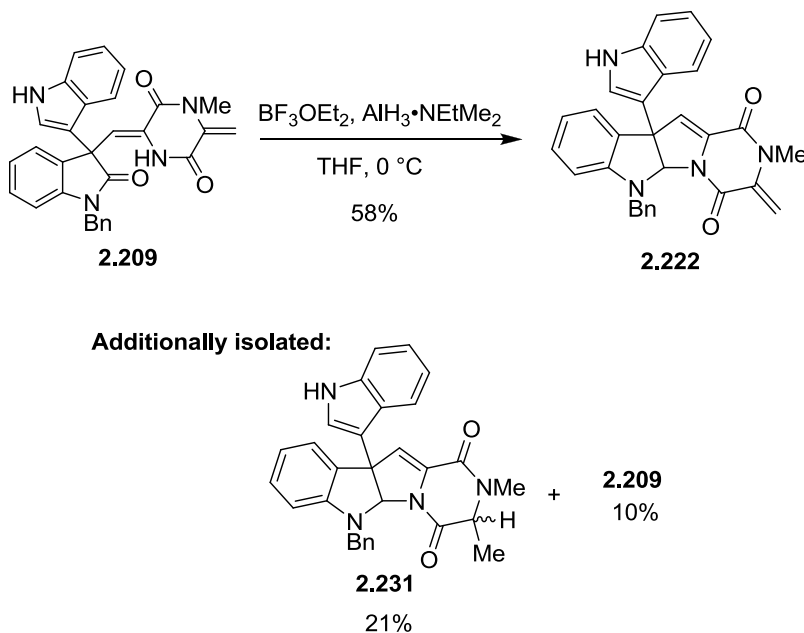
In order to probe these important questions, oxindole **2.209** was mixed with an assortment of Lewis acids, including BF₃•OEt₂, AlEt₃, and TMSOTf, and a reducing agent was added. The reducing agents screened were AlH₃•Me₂NEt, AlH₃, LiBHET₃, and LAH (Scheme 2.58). From these experiments, it appears that the addition of a Lewis acid is critical to gaining selectivity for the reductive coupling. The presence of BF₃OEt₂, AlEt₃ or TMSOTf led to the production of isolable quantities of **2.222**. The best condition involved premixing oxindole **2.209** and BF₃OEt₂ followed by adding AlH₃•Me₂NEt at -50 °C to give **2.222** in 41% yield. Use of AlEt₃ and TMSOTf as Lewis acids gave **2.222** in lower yields and if no Lewis acid was present, no trace of **2.222** was observed. When BF₃OEt₂ or AlEt₃ was used, the reaction was generally clean, leading mostly to **2.222** and recovered starting material **2.209**. The reaction always halts between 15-40% conversion as judged by TLC. The product **2.222** slowly decomposes under the reaction conditions, so it was necessary to quench the reaction once the conversion halted. Variations of solvent had no effect on the conversion.

Scheme 2.58: Screening of various Lewis acids and reducing agents to access **2.222**



We identified conditions for reductive cyclization of **2.209** by careful optimization of reaction variables (Scheme 2.59). Namely, **2.209** was premixed with 1.5 equivalents of BF_3OEt_2 in THF and $\text{AlH}_3\cdot\text{Me}_2\text{NEt}$ was added dropwise at 0 °C when the reaction was quenched with dilute acetic acid after 1 minute, we could reproducibly isolate the key hexacyclic core structure **2.222** in 54-58% yield. We also isolated 21% yield of the over-reduced product **2.231** as a mixture of diastereomers; the starting material was present in 10% yield. A more comprehensive screening of Lewis acids may avoid the formation of **2.231** and improve the yield.

Scheme 2.59: Optimized reductive coupling conditions



At this point, we were reasonably confident that the compound isolated was indeed the desired hexacyclic core structure **2.222**, but the H^1 NMR and C^{13} NMR data were somewhat ambiguous. The high-resolution mass spectrum was consistent with **2.222**, but the possibility that this compound was a related structural isomer was a concern. All attempts to recrystallize **2.222** were unsuccessful. Thus, we tried to derivatize **2.222** in such a way that would confirm its structure. The putative tetracycle **2.222** was hydrogenated using palladium on carbon under an atmosphere of hydrogen. Over the course of 12 h, a number of products were isolated and characterized (Scheme 2.60). The first reduction occurred at the exocyclic olefin, leading to a mixture (3:1) diastereomers **2.232** and **2.233**. Prolonged exposure of **2.232** and **2.233** to the reaction conditions led to the reduction of the internal olefin. Substrate **2.233** was reduced selectively, with the hydrogenation occurring on the proximal face to the methyl group,

giving isomer **2.234** as the sole product, whereas **2.232** was reduced without any facial selectivity, giving a mixture (1:1) of isomers **2.235** and **2.236**. The structure of isomer **2.234** was established by X-ray crystallography, thus confirming that we began with the hexacyclic starting material **2.222** (Figure 2.11).

Scheme 2.60: Structural elucidation of **2.150** by characterization of derivatives

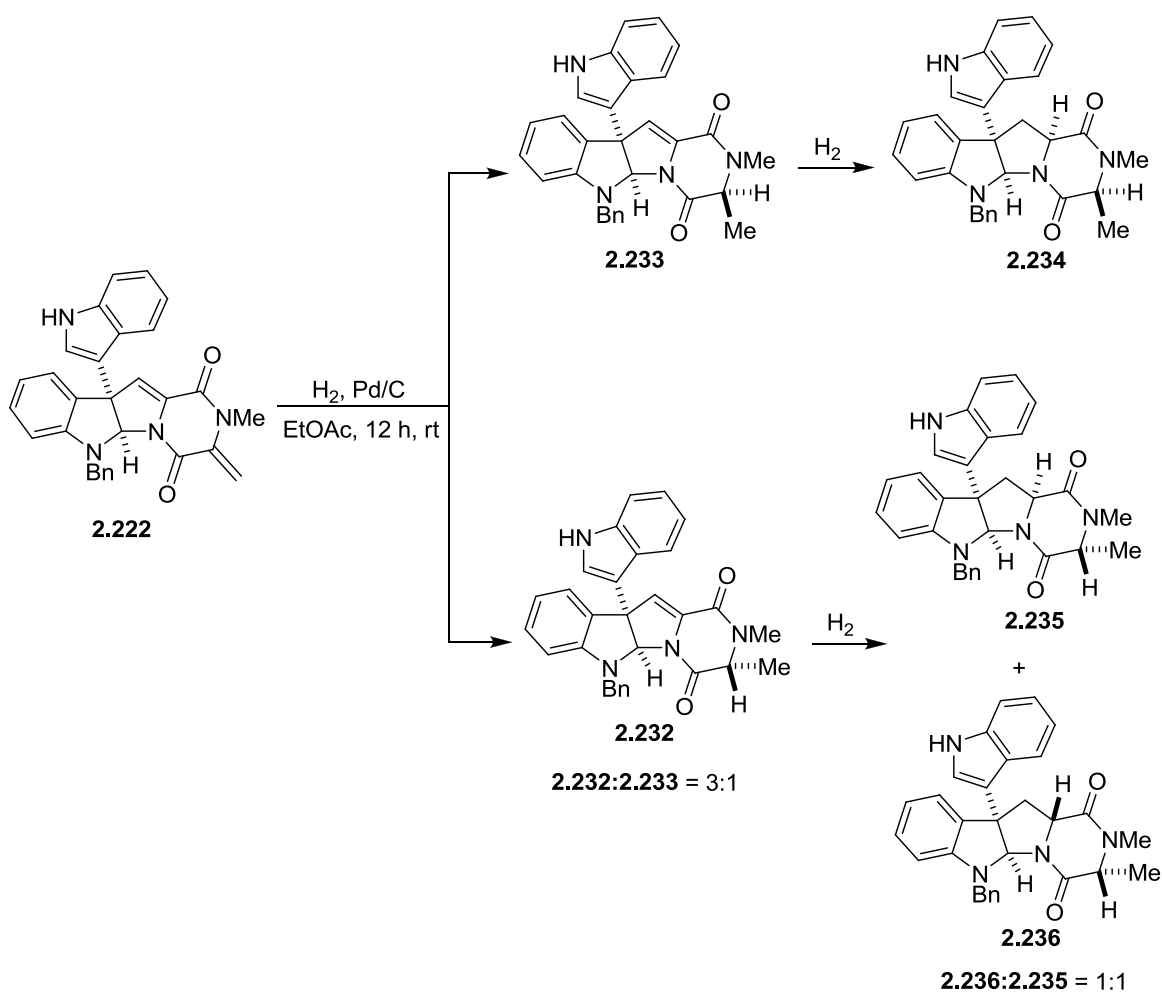
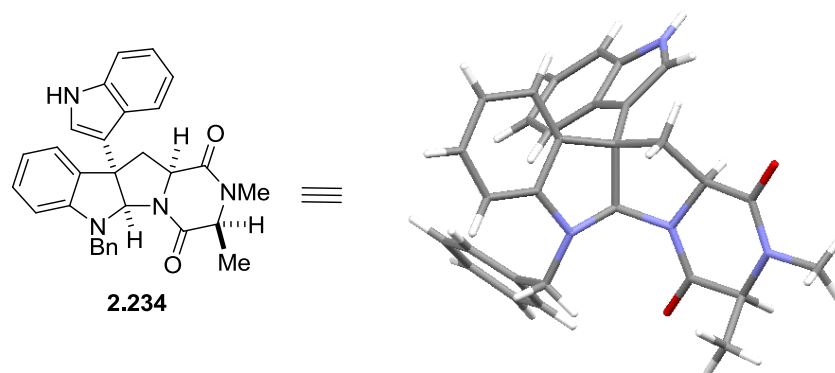


Figure 2.11: X-ray crystal structure of hydrogenated derivative **2.234**.

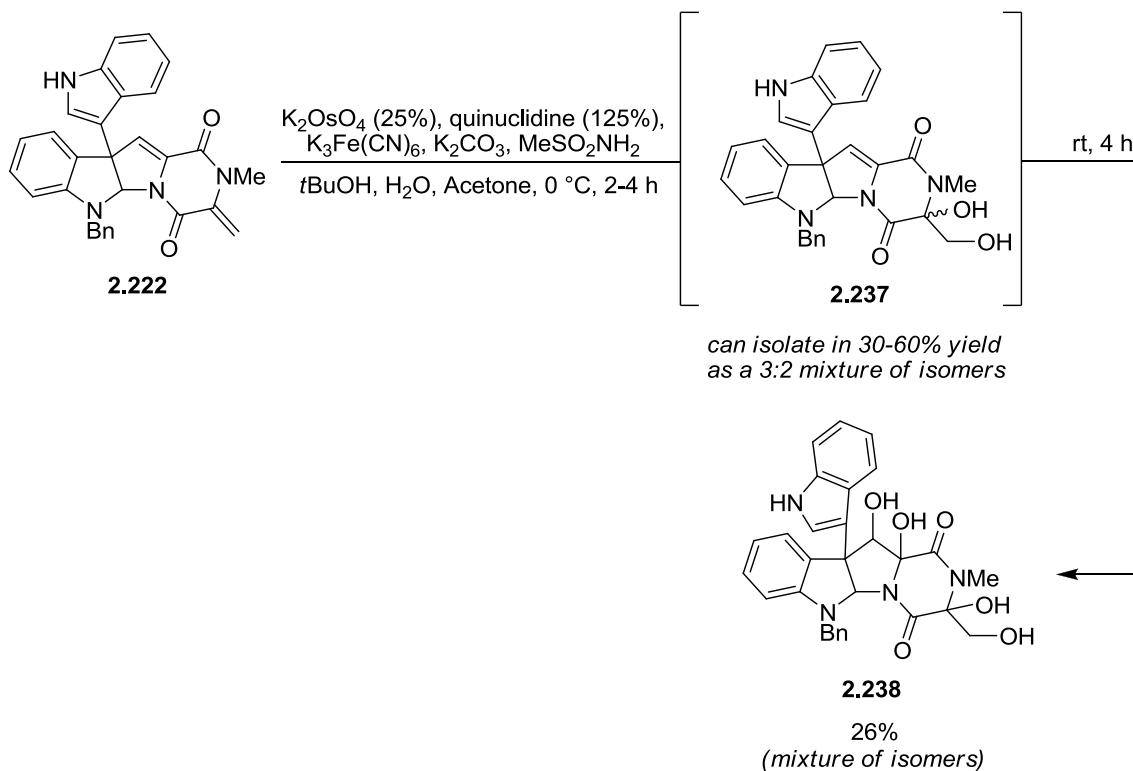


2.3.1.5. Oxidation of diene **2.222**

With core structure **2.222** in hand, we began to explore methods to effect the double dihydroxylation of the two olefins of **2.222**. The first conditions that we screened were similar to those developed by Overman in his total synthesis of gliocladiene C.¹²³ By mixing diene **2.222** with K₂OsO₄, quinuclidine, K₃Fe(CN)₆, K₂CO₃, and MeSO₂NH₂ under biphasic conditions at 0 °C, we saw rapid oxidation of the external olefin leading to diol **2.237** as a mixture (3:2) of two isomers (Scheme 2.61). Continued stirring led to tetraol **2.238** in 26% yield as a mixture of three isomers, along with 10-15% of the mono-oxidized product **2.237**. A mixture of unidentified side products was also isolated from the reaction accounting for 25-50% of the mass recovery. If the reaction was halted after the first oxidation, diol **2.237** can be isolated in 30-60% yield depending on the conditions. Upon continued exposure to the oxidizing conditions, the diol **2.237** and tetraol **2.238** degrade into an intractable mixture of unidentified side products, most likely accounting for the low yields. Attempts were made to alter these conditions to achieve

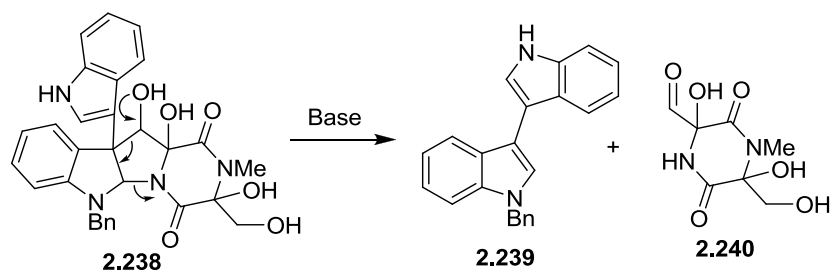
better yields by modifying the pH of the reaction, changing the solvents, and using different oxidants, but all modified conditions resulted in lower yields of tetraol **2.238**.

Scheme 2.61: Double dihydroxylation of **2.222**



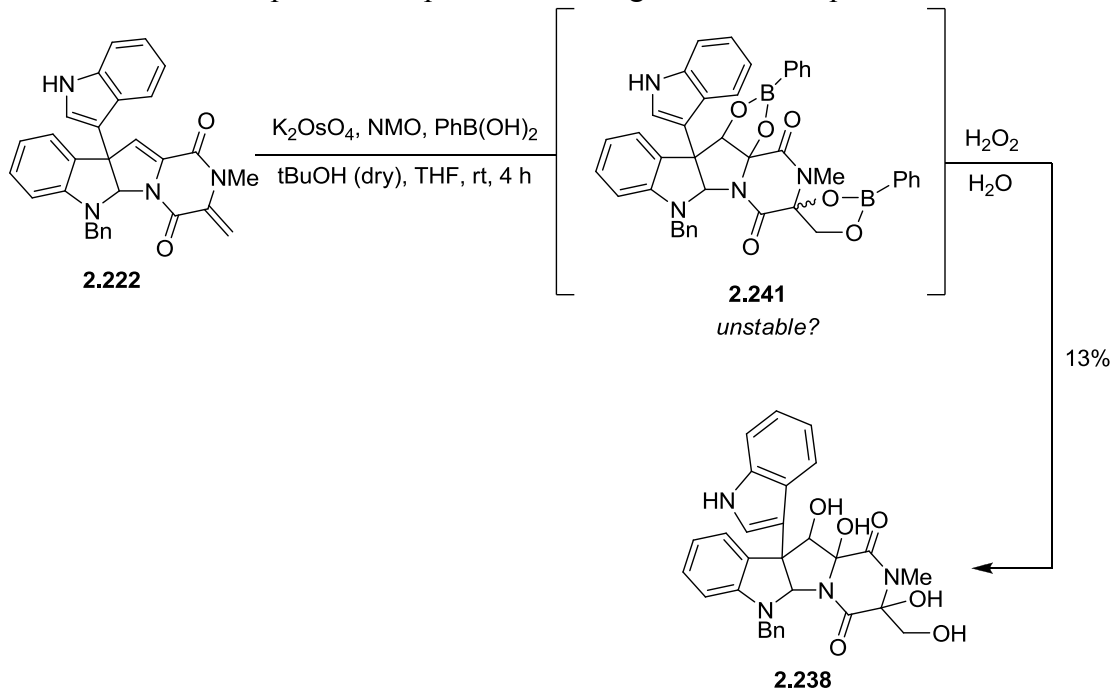
When monitoring this oxidation by TLC, it appeared that the initially formed diol **2.237** was stable to the reaction conditions, whereas the tetra-hydroxylated product **2.238** was not. We hypothesized that one potential side reaction might involve fragmentation of the tetrahydroxylated compound **2.238** to give bis-indole **2.239** and aldehyde **2.240** (Scheme 2.62).¹⁹⁷ Masses consistent with **2.240** and **2.239** were observed by LCMS; but we were not able to isolate either one of these compounds from the reaction.

Scheme 2.62: Possible fragmentation pathway leading to the instability of **2.238**.



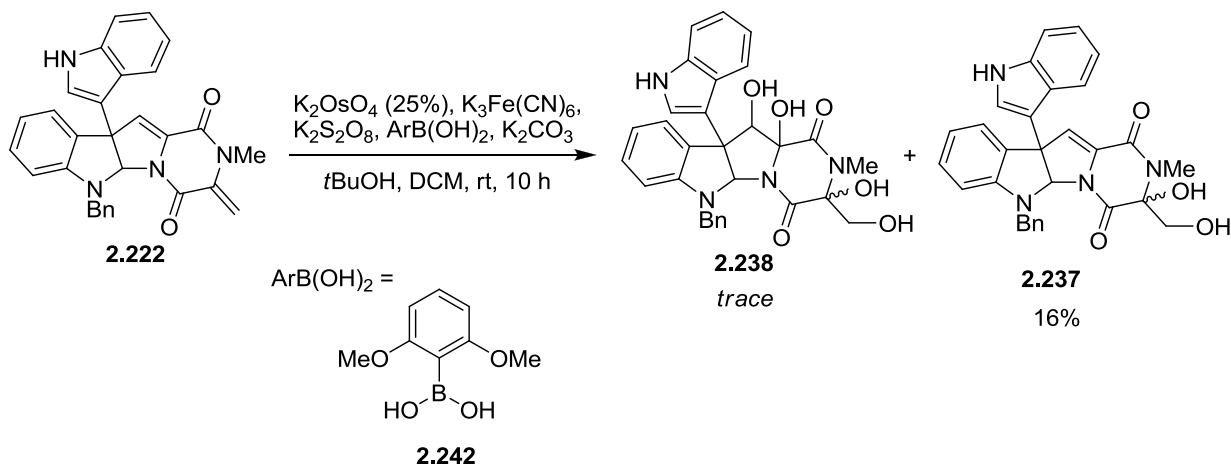
In an effort to prevent this presumed side-reaction, we were inspired by a protocol developed by Narasaka and later improved by Sharpless, wherein the dihydroxylation is carried out under anhydrous conditions in the presence of phenylboronic acid.^{198,199} The boronic acid hydrolyzes the intermediate osmate ester, forming a boronic ester **2.242** rather than a diol. When we applied similar conditions to **2.222**, we observed an increase in the rate of consumption of **2.222** (Scheme 2.63), but, **2.238** was isolated in only 13% yield after oxidative workup.

Scheme 2.63: Attempted *in-situ* protection during the oxidation procedure



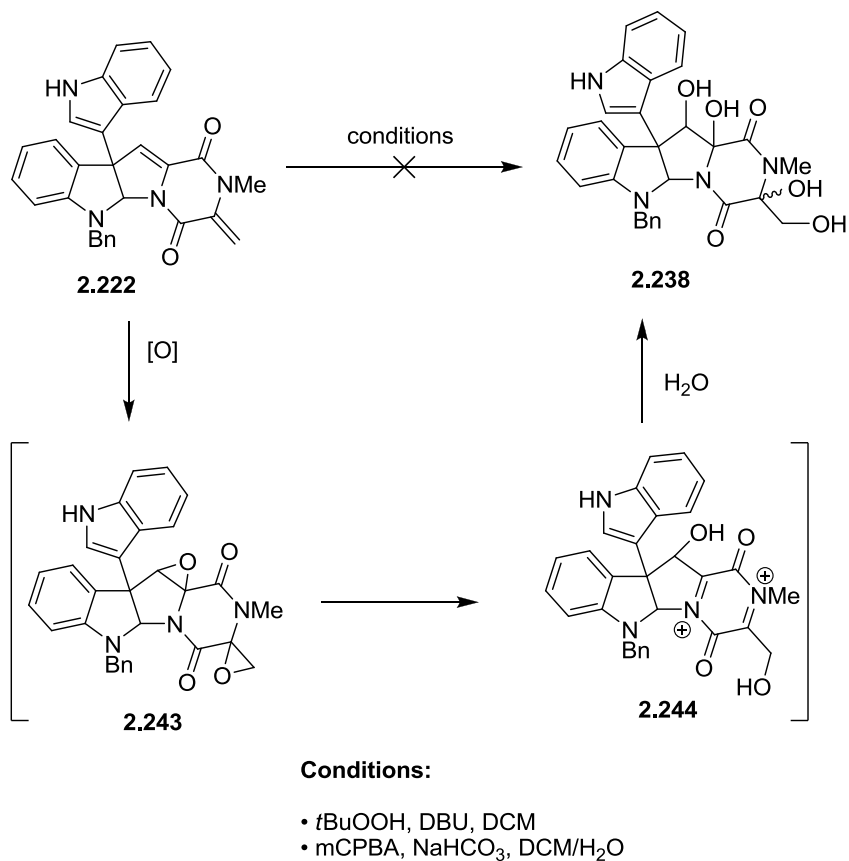
We were unable to isolate any boronate esters intermediates, thus we hypothesized that the difficulties with the reaction may be due to the instability of intermediates such as **2.241** to hydrolysis. We sought a more stable boronic ester by screening similar reaction conditions, using the more electron-rich *ortho*-methoxy substituted boronic acid **2.242**, as we hoped that boronic esters would be more stable to hydrolysis because of a less electrophilic boron center (Scheme 2.44). Unfortunately, the results using boronic acid **2.242** were even worse, giving the desired hydroxylated product **2.238** in only trace amounts.

Scheme 2.64: In-situ boronic ester formation using alternate boronic acid **2.242**.



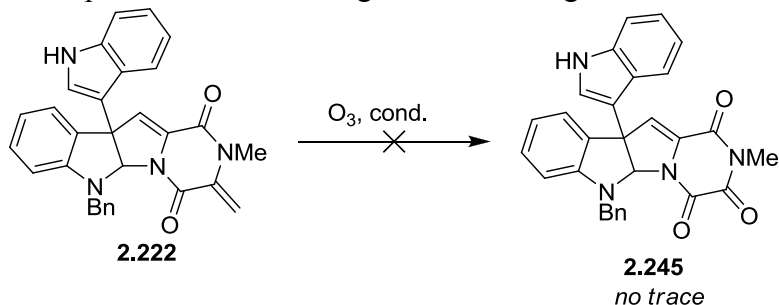
We also tried to oxidize **2.222** to **2.238** via the epoxide intermediate **2.243**, thinking that bis-epoxide **2.243** would be prone to spontaneous ring-opening to a reactive iminium species such as **2.244**, which would be trapped by water to give **2.238**. However, nucleophilic epoxidation conditions using *tert*-butyl hydroperoxide and DBU led to an intractable mixture of products (Scheme 2.65), whereas oxidation using mCPBA with buffer in biphasic conditions resulted in what we believe to be oxidation of the indole ring based on LCMS and ^1H NMR. In both cases, we failed to detect even trace amounts of **2.238**.

Scheme 2.65: Attempted epoxidations to access **2.238**



It was previously observed that the external olefin of **2.222** oxidizes much more rapidly than the internal olefin (Scheme 2.61). This finding led to us to explore the oxidative cleavage of the exocyclic olefin of **2.222** to access the gliocladin C skeleton **2.245**. However, attempted selective ozonolysis led to over oxidation of the starting material; we never detected any trace of desired product **2.245** (Scheme 2.66).

Scheme 2.66: Attempted oxidative cleavage of **2.222** using ozone

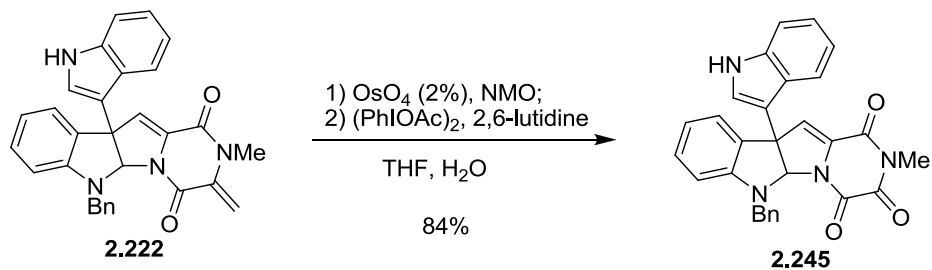


conditions:

- O_3 (3 eq), $-78\text{ }^\circ\text{C}$, acetone/ H_2O
- O_3 (3 eq), 2,6-lutidine, pyridine, $-78\text{ }^\circ\text{C}$, acetone/ H_2O

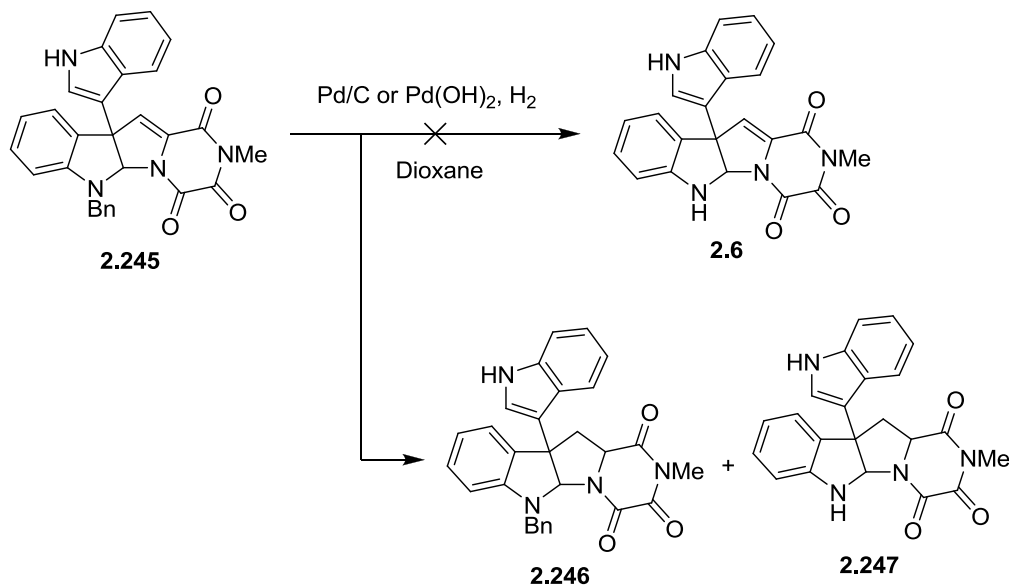
When diene **2.222** was exposed to Johnson-Lemieux conditions in the presence of 2,6-lutidine, **2.245** was isolated in 7% yield, along with 55% recovered starting material.^{200,201} However, oxidative cleavage of **2.222** was accomplished by using osmium tetroxide (2 mol %), phenyl iodoacetate, *N*-methylmorpholine oxide, and 2,6-lutidine, giving **2.245** in 84% yield (Scheme 2.67).²⁰² Hexacyclic compound **2.245** was identified on the basis of on ^1H NMR, ^{13}C NMR, and HRMS.

Scheme 2.67: Improved oxidative cleavage conditions using NMO and $\text{PhI}(\text{OAc})_2$.



With the oxidative cleavage conditions developed, we could explore tactics to elaborate **2.245** into gliocladin C (**2.6**) by the removal of the *N*-benzyl group. It should be noted that the synthesis was originally planned to target only the oxidized epipolythiodiketopiperazine containing natural products such as **2.9** and **2.12**, so we did not anticipate the need for removal of the *N*-benzyl group in the presence of a trisubstituted olefin. Subjecting **2.245** to hydrogenative conditions with Pd/C or Pd(OH)₂ failed to produce isolable amounts of gliocladin C. Under all conditions screened, the first product formed was **2.246** as identified by LCMS monitoring of the reaction mixture (Scheme 2.68). Continued reaction time led to varying amounts of the reduced debenzylated product **2.247** as identified by LCMS monitoring of the reaction mixture. Use of Pd(OH)₂ led to faster hydrogenation of both the internal olefin and the benzyl group. Addition of protic acids such as AcOH, TFA, and HCl did not affect the rate of benzyl group hydrogenolysis versus olefin hydrogenation. Preliminary attempts to debenzylate **2.245** under reducing metal conditions were also unsuccessful.

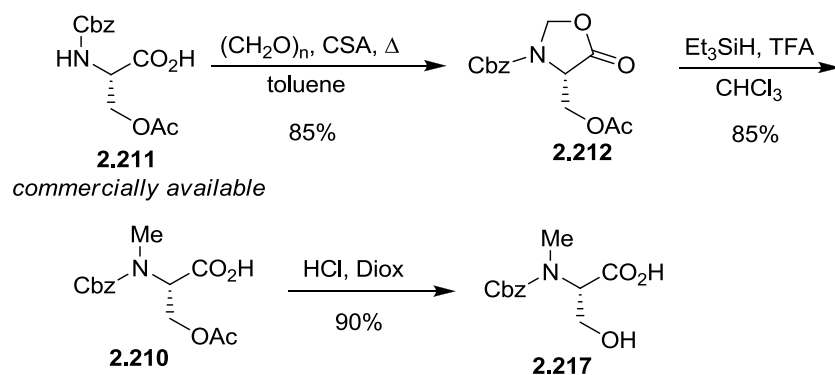
Scheme 2.68: Attempted benzyl group removal under hydrogenolysis conditions



In summary, the synthesis of *N*-benzyl gliocladin C (**2.6**) was accomplished in 9 total steps and 13.4% overall yield from commercially available **2.11** by a novel and concise route, starting from simple and readily available starting materials. If **2.245** were elaborated to Gliocladin C (**2.6**), this route would compare favorably to the routes from Overman (14 steps, 14.4% yield) and Movassaghi (14 steps, 10.7% yield).

The overall sequence is summarized in Scheme 2.269-2.271. Commercially available protected serine derivative (**2.211**) was converted in 3 simple steps to *N*-methyl-amino acid **2.217** (Scheme 2.69). This sequence required no chromatography and is easily scalable to produce large amounts of **2.217**.

Scheme 2.69: Five step route from serine protected N-methyl-amino acid **2.217**.

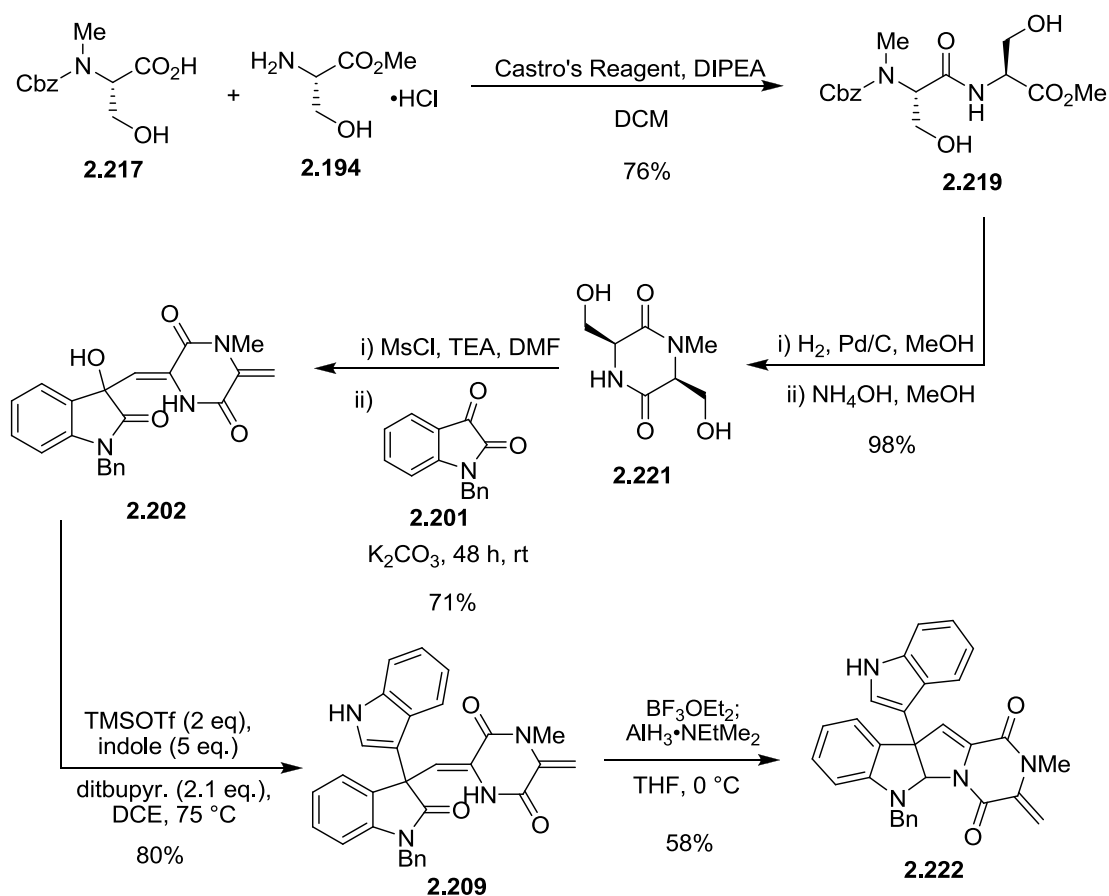


A coupling procedure was developed for coupling of **2.217** and **2.194** using Castro's reagent to give **2.219** in 76% yield. Dipeptide **2.219** was deprotected and cyclized in a high-yielding transformation to give diketopiperazine **2.221** (Scheme 2.70). One of the featured steps in the route to **2.245** is the unprecedented one-pot activation, elimination, and nucleophilic addition of **2.221** to isatin **2.201** that was initiated by treatment of **2.221** with MsCl and K_2CO_3 in DMF to furnish 3-hydroxyindole **2.202** in 71% yield. The use of unsaturated diketopiperazines as nucleophiles is a valuable new synthetic tool for the construction of diketopiperazine containing natural products because of it is a short and convergent approach that uses readily available starting materials. Additionally, this step serves as a potential branching point to introduce diversity for the synthesis of analogues by replacing **2.201** with a variety of isatin derivatives.

The Lewis acid promoted ionization of **2.202** presence of indole gave the disubstituted oxoindole **2.209** in 73% yield. This transformation constitutes a useful

expansion over the previously reported ionization of tertiary bromide **2.43** to give **2.45**. A system for the selective reductive cyclization were eventually discovered by using a reducing agent in the presence of a Lewis acid activator, allowing for the construction of the key hexahydropyrroloindoline core skeleton **2.222** in five steps from peptide **2.217** and commercially available serine methyl ester **2.194**. This novel set of conditions may find future applications in the reductive cyclization of substrates with sensitive functionality such as unsaturated amides, esters, and ketones.

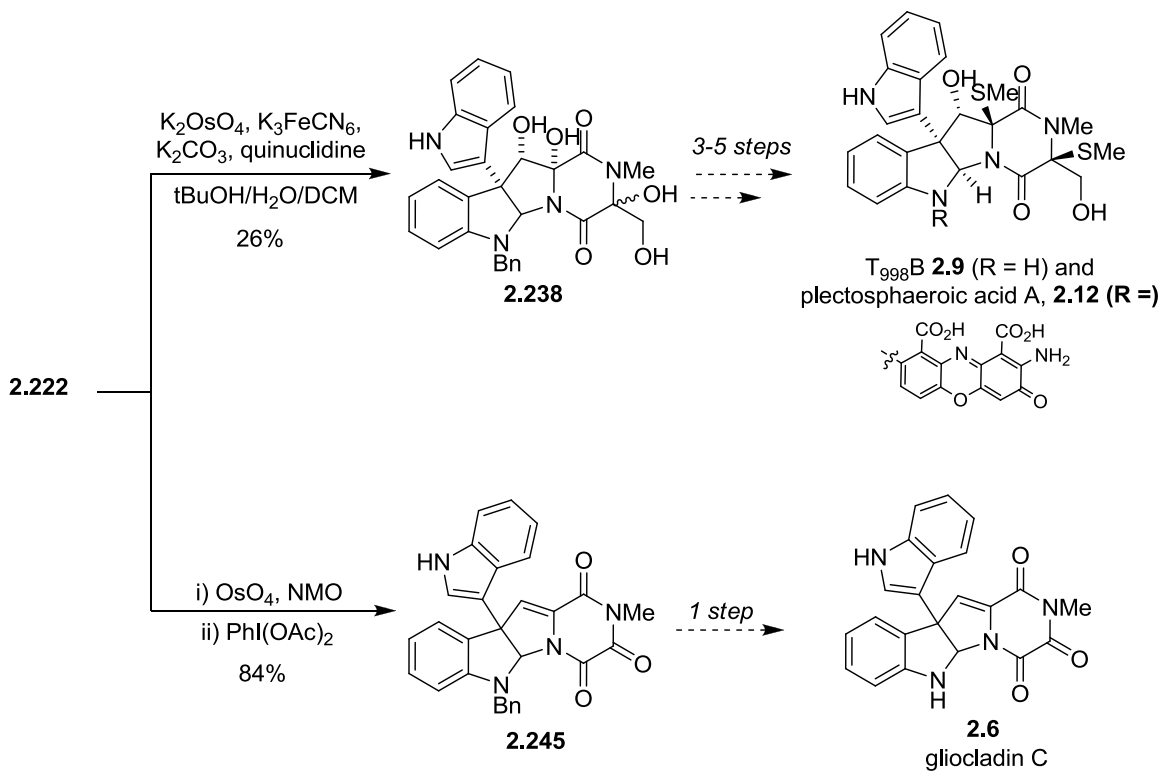
Scheme 2.70: Synthesis of diketopiperazine **2.221** and formation of core structure **2.222**



The core structure **2.222** can be elaborated in two ways. One is by the double dihydroxylation to give tetraol **2.238**. This transformation has been accomplished by using a modified version of the Sharpless conditions to give **2.238** in 26% yield as a mixture of isomers (Scheme 2.71). If **2.238** could be accessed more selectively it would be an estimated 3-5 steps removed from a number of natural products within the epipolythiodiketopiperazine containing natural product family that have never before synthesized, including T998B (**2.9**) and plectosphaeroic acid A (**2.12**).

Furthermore, the exocyclic olefin of **2.222** can be oxidatively cleaved to give *N*-benzyl-gliocladin C (**2.245**). Upon development of the debenzylation conditions, this will constitute a total synthesis of gliocladin C (**2.6**). In the instance that the *N*-benzyl group of **2.245** cannot be removed, the route can be modified slightly to use an alternate isatin electrophile with a more suitable protecting group such as PMB or SEM. Additional advancement may include the development of an enantioselective variant, most likely employing a chiral Lewis acid for the ionization of **2.202** going to **2.209**.^{152,153}

Scheme 2.71: Final elaborations into hexahydropyrroloindoline natural products

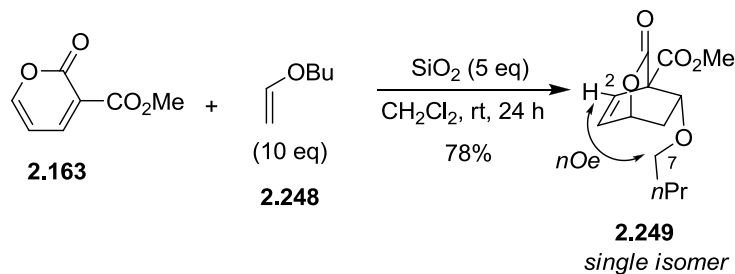


2.3.2. RESULTS AND DISCUSSION: MPC1001 CORE STRUCTURE *VIA* RETRO HOMO-DIELS-ALDER CYCLOADDITION OR BY COPE REARRANGEMENT OF DIVINYL EPOXIDES

2.3.2.1. Sequential pyrone cycloaddition and retro-homo Diels-Alder cycloaddition

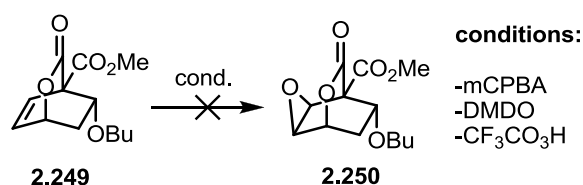
Our interest in the dihydrooxepine epipolythiodiketopiperazine alkaloids inspired efforts directed toward developing new methods for the construction of fused dihydrooxepins. We envisioned two potential approaches to access the dihydrooxepin core of these alkaloids. The first of these would involve a sequential pyrone cycloaddition and retro-homo Diels-Alder cycloaddition (Scheme 2.29) and the second by a Cope rearrangement of a divinyl epoxide (Scheme 2.33). We initiated work on a model system for the retro homo-Diels-Alder reaction by reacting carbomethoxy pyrone **2.163** with vinyl *n*-butylether (**2.248**). Pyrone **2.163** was selected for this study because it is commercially available, or it can be synthesized in two steps from inexpensive starting materials.²⁰³ Additionally, **2.163** was well-known to undergo Diels-Alder reactions with a variety of olefinic partners with high selectivity.²⁰⁴ In the event, we found that the Diels-Alder of **2.163** with **2.248** gave **2.249** in 78% yield as a single isomer (Scheme 2.72). The structural assignment was made basis on the nOe interactions of the C7 *n*butyl group protons (3.34 ppm) and the proximal C2 vinylic proton (6.79 ppm). The selectivity that we observed matches what is reported for similar systems.²⁰⁴

Scheme 2.72: Diels-Alder to synthesize bicyclic lactone **2.249**.



Attempts to epoxidize **2.249** to **2.250** with mCPBA, DMDO, and trifluoroperacetic acid failed consume the starting material (Scheme 2.73). After prolonged heating, the starting material began to decompose to a complex mixture of side-product. The unreactive nature of the olefin may be due to its electron deficiency.

Scheme 2.73: Attempted epoxidation of **2.249**.



After an extensive screening of conditions in attempts to form halohydrin **2.251**, we found that **2.249** was consumed by exposure to trichloroisocyanuric acid (TCCA) (**2.253**) or tribromoisocyanuric acid (TBCA) (**2.254**) in the presence of triflic acid (Scheme 2.74). However, the reaction of **2.249** with TCCA in dioxane/H₂O gave a mixture (1:1) of the rearranged chlorohydrins **2.255** and **2.256** in 70% yield (equation 2.7). Similarly, reaction of **2.249** with TBCA in the presence of triflic acid gave the unexpected bromohydrin **2.257** in 83% yield (equation 2.8). The structures of **2.255** and **2.256** were confirmed by X-ray crystallography (Figure 2.12).

Scheme 2.74: Halohydrin formation conditions and TBCA.

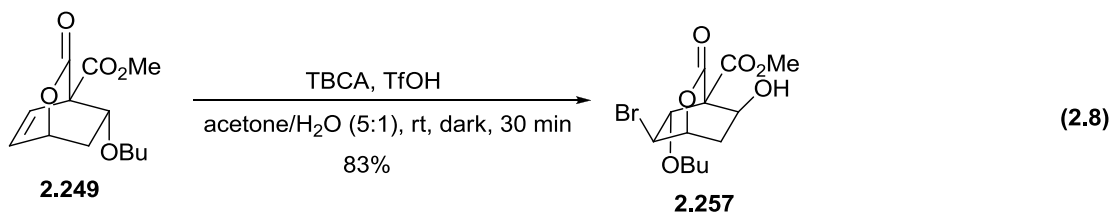
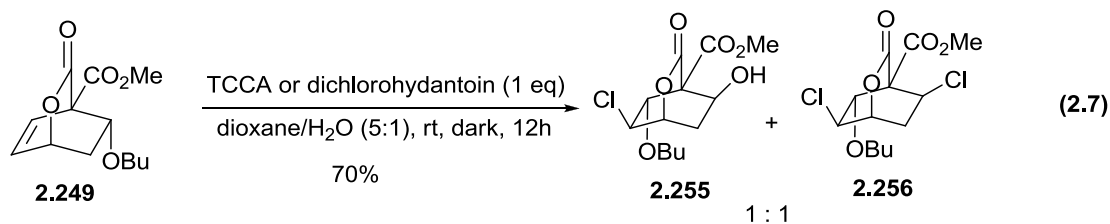
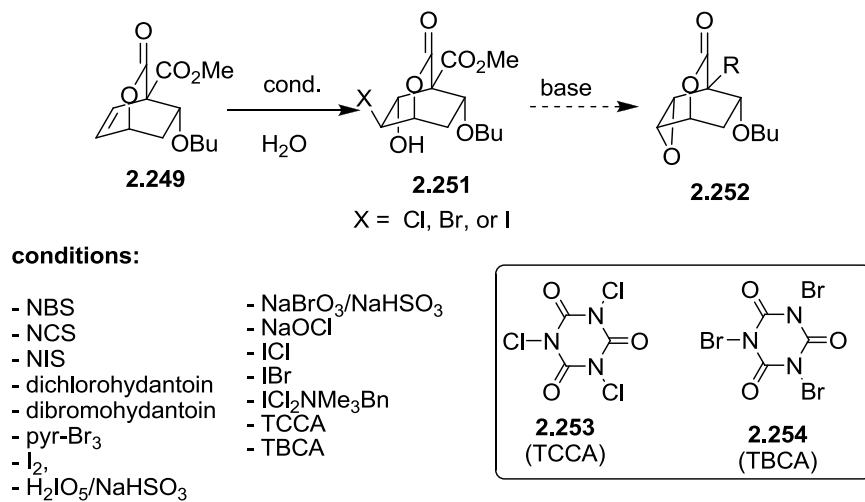
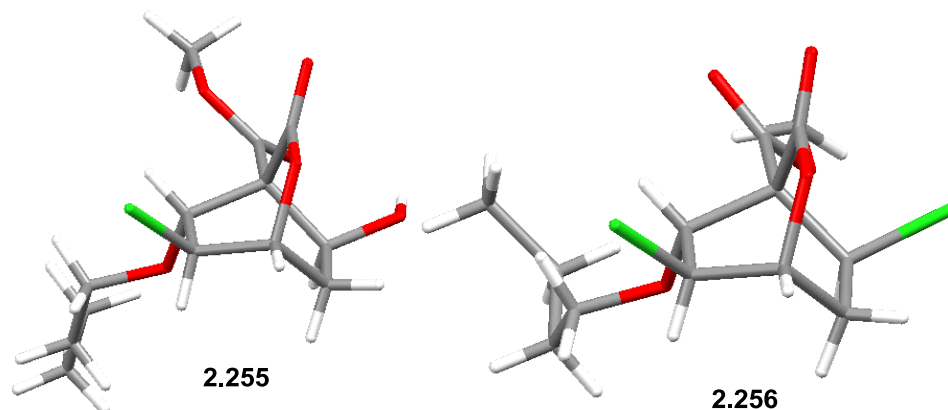
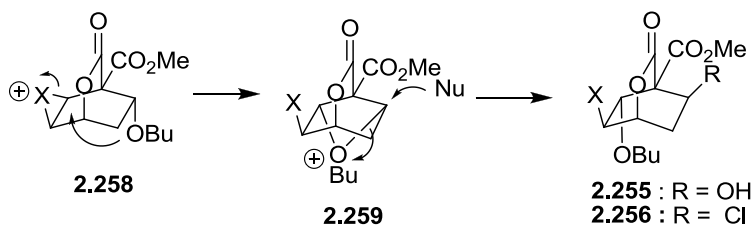


Figure 2.12: X-ray crystal structures of **2.255** and **2.256**



The formation of products **2.255**, **2.256** and **2.257** can be explained by the cyclization displacement of the initially formed halonium ion **2.258** with the adjacent ether oxygen atom to give an oxonium intermediate **2.259** that was susceptible to nucleophilic displacement by water or halide, giving the observed products **2.255** or **2.256** (Scheme 2.75).²⁰⁵

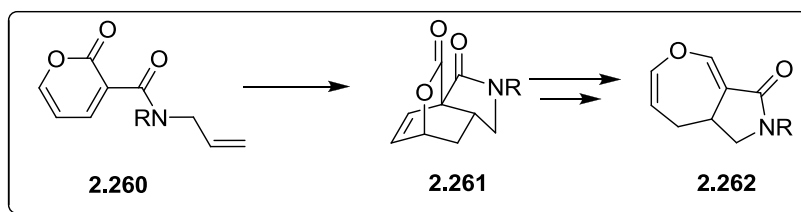
Scheme 2.75: Mechanistic explanation for the observed products.



In order to avoid this undesired rearrangement during the halohydrin formation, we designed a model system lacking any nucleophilic heteroatoms on the *endo* face of

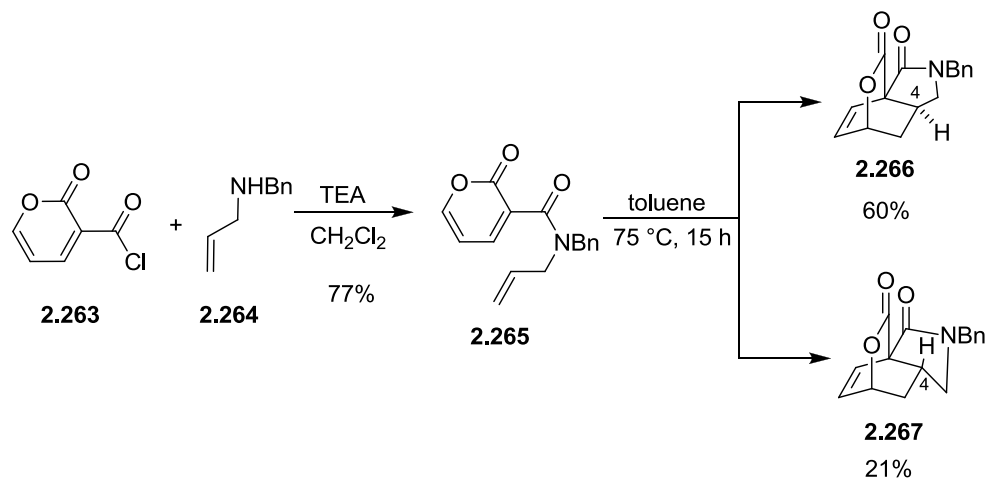
the molecule (Scheme 2.76). An intramolecular Diels-Alder reaction with allylamide **2.260** would provide the tricyclic ester **2.261**, epoxidation of which thermal extrusion of carbon dioxide might allow us access bicyclic oxepins such as **2.262**.

Scheme 2.76: Proposed model system to avoid unwanted rearrangements



Given this plan, the known pyrone acid chloride **2.263** was added to a solution of allyl amine **2.264** and triethylamine to give amide **2.265** in 77% yield (Scheme 2.77). Pyrone **2.265** was then heated in toluene at 75 °C to provide the *exo*-cycloadduct **2.266** in 60% yield and the *endo*-cycloadduct **2.267** in 21% yield after separation by flash chromatography. The *endo* and *exo* structural designations for **2.266** and **2.267** were retroactively assigned based on X-ray crystal structure of **2.268** (Figure 2.13). The *exo*-isomer **2.266** and *endo*-isomer **2.267** can be distinguished by the characteristic shifts of their C4 protons at 2.24 ppm and 2.60 ppm, respectively. Efforts to improve the diastereoselectivity of the cycloaddition with Lewis or Brønsted acid catalysis failed to show any significant enhancement to the ratio of **2.266** to **2.267**.

Scheme 2.77: Intramolecular [4+2] cycloaddition



The *exo*-cycloadduct **2.266** was subjected to TBCA and triflic acid in an acetone/water mixture to furnish bromohydrin **2.268** in 78% yield (equation 2.9). The structure of **2.268** was confirmed by X-ray crystallography (Figure 2.13). *Endo*-cycloadduct **2.267** was reacted under identical conditions to give the bromohydrin **2.269** in 19% yield (equation 2.10). The regio- and stereochemical structural assignments of **2.269** were made based on analogy to those observed with **2.268**. The stereochemistry of the bromohydrin reflects the formation of the bromonium on the less hindered face of the double bond proximal to the lactone bridge, followed by nucleophilic attack of water from opposite face. The regiochemistry of the bromohydrin results from the nucleophilic addition of water to the more electropositive carbon of the bromonium, proximal to the electron withdrawing amide and lactone.

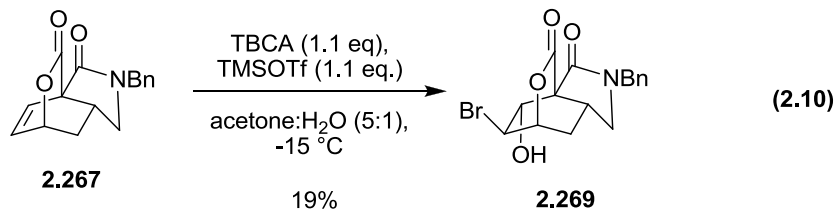
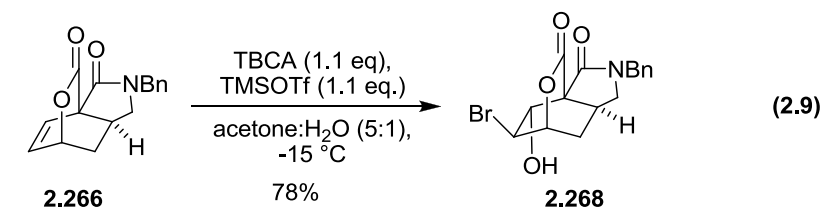
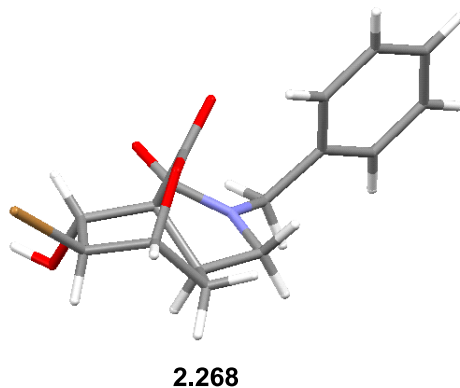


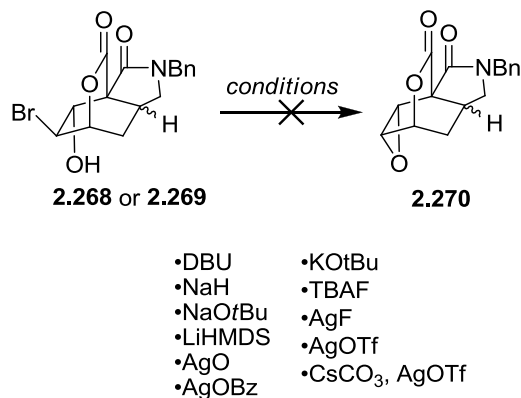
Figure 2.13: X-ray crystal structure of **2.268**



Bromohydrins **2.268** and **2.269** were subjected to a variety of basic conditions in attempts to access *endo*-epoxide **2.270** (Scheme 2.78), but they were unreactive, even under forcing conditions. When **2.268** and **2.269** were heated, the starting material decomposed to an intractable mixture of side products; no trace of **2.270** was ever

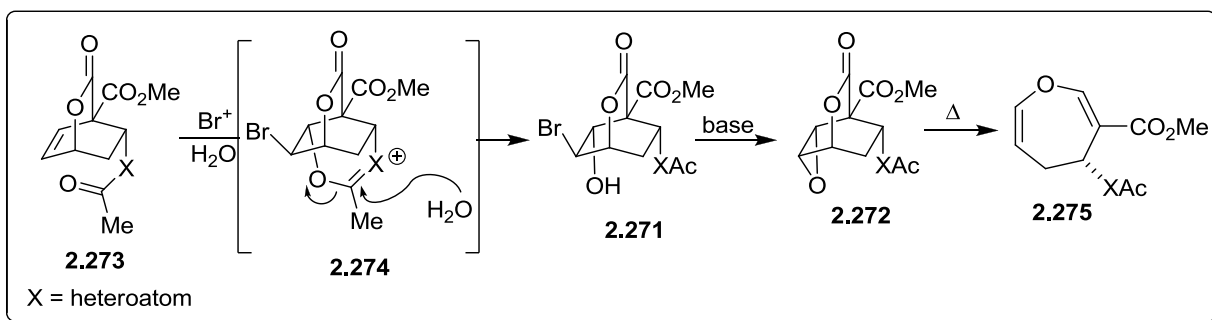
detected. We suspected that the failure of bromohydrins **2.268** and **2.269** to react may be due to the highly strained nature of tetracycle **2.270**.

Scheme 2.78: Failed epoxide formation



We hoped that the halohydrin **2.271** would allow for the closure to the epoxide **2.272** due to a lower amount of strain in the tricyclic product. In order to test this hypothesis, we examined an approach wherein we would synthesize a bicyclic ester shown by **2.273**. We speculated that the acyl group oxygen atom may participate during the bromination through a cyclic oxonium species such as **2.274**, which may hydrolyze to give **2.271** (Scheme 2.79). Exposure to base would lead to epoxide **2.272** and then Cope rearrangement would then lead to substituted oxepin **2.275**.

Scheme 2.79: Synthesis of bicyclic bromohydrin **2.271**



Efforts to synthesize a bicyclic ester such as **2.273** began with a screening of vinyl acetate **2.276** and *N*-acyl vinyl amides **2.277** and **2.278** in the cycloaddition with 2-carbomethoxy pyrone (**2.263**) (Scheme 2.80); only *N*-Vinyl pyrrolidone **2.278** underwent a [4+2] cycloaddition with **2.263** in the presence of catalytic Yb(OTf)₃ (1 mol %) at room temperature to give the cycloadduct **2.279**, the structure of which was confirmed by X-ray crystallography (Figure 2.14).

Scheme 2.80: Screening of dienophiles

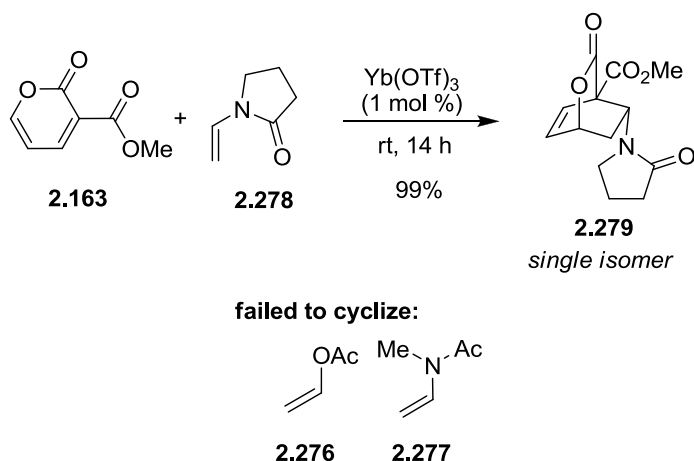
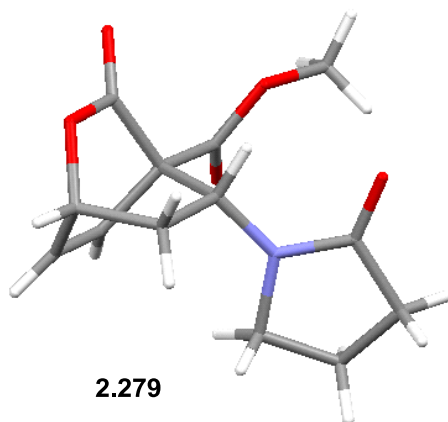
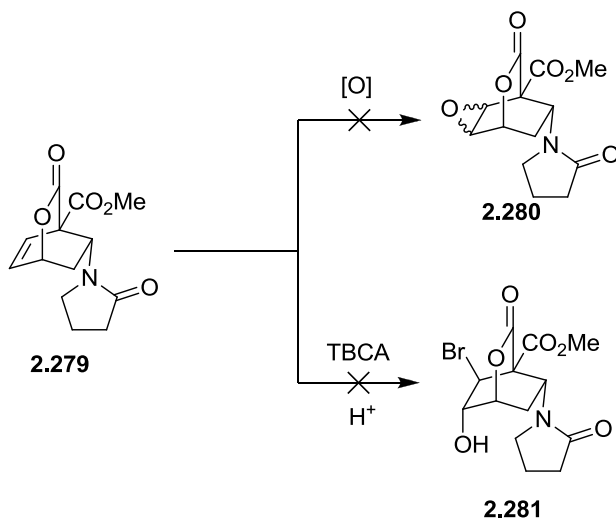


Figure 2.14: X-ray crystal structure of **2.279**



We then explored the direct oxidation of cycloadduct **2.279** using a number of oxidants including mCPBA, trifluoroperacetic acid, and methyl trifluoromethyl dioxirane, all of which gave recovered **2.279** (Scheme 2.81). Heating the reactions generally resulted in the decomposition of the starting material to a complex mixture of products. Similarly, exposure of **2.279** to TBCA under acidic conditions with either HCl or triflic acid gave mostly recovered **2.279**. No trace of the desired bromohydrin **2.281** was detected.

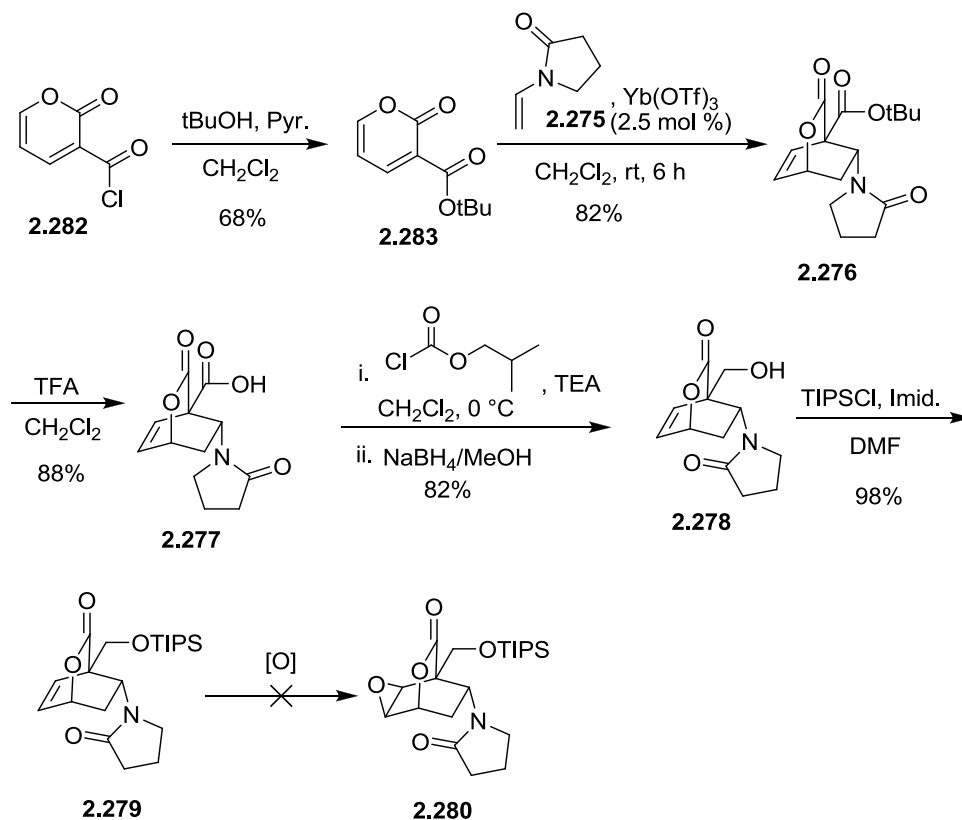
Scheme 2.81: Attempted oxidation of electron deficient olefin **2.279**



In an effort to make the olefin in **2.279** less electron deficient, we explored the reduction of the exocyclic methylester to an alcohol. However, attempts to reduce the exocyclic ester of **2.279** failed to give any trace of the desired product (Scheme 2.82). Accordingly, we were compelled to pursue a more circuitous approach to synthesize the alcohol. The acid chloride **2.282** was thus esterified with *tert*-butanol to give pyrone **2.283** in 68% yield.²⁰³ Diels-Alder cycloaddition of **2.283** with vinyl pyrrolidone **2.275** in the presence of a catalytic amount of $Yb(OTf)_3$ furnished cycloadduct **2.276** in 82% yield. Exposure of **2.276** to trifluoroacetic acid cleanly gave the free acid **2.277** in 88% yield. The mixed anhydride obtained by reaction of **2.277** with isobutyl chloroformate was reduced with sodium borohydride to furnish the alcohol **2.278** in 82% yield. Protection of the hydroxyl group with TIPSCl and imidazole provided TIPS-ether **2.279** in 98% yield. When **2.279** was then exposed to mCPBA, trifluoroperacetic acid, and methyl trifluoromethyl dioxirane; no trace of the desired epoxide **2.280** was detected.

After prolonged exposure to the reaction conditions or heating, loss of the –TIPS group was observed, but no epoxide was isolated.

Scheme 2.82: Synthetic route to access **2.280**.



On the other hand iodohydrin **2.281** was formed in 90% yield by the action of *N*-iodosuccinimide and trifluoroacetic acid (Scheme 2.83); no conversion was observed without the addition of acid. The structure of **2.281** was confirmed by X-ray crystallography (Figure 2.15).

Scheme 2.83: Synthesis of iodohydrin **2.281**.

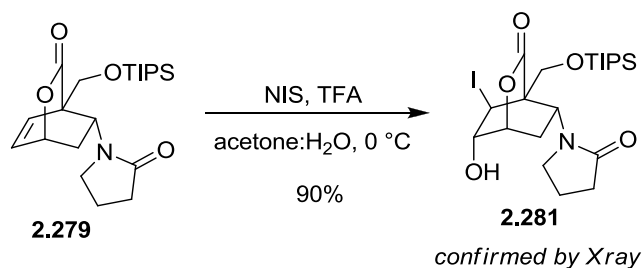
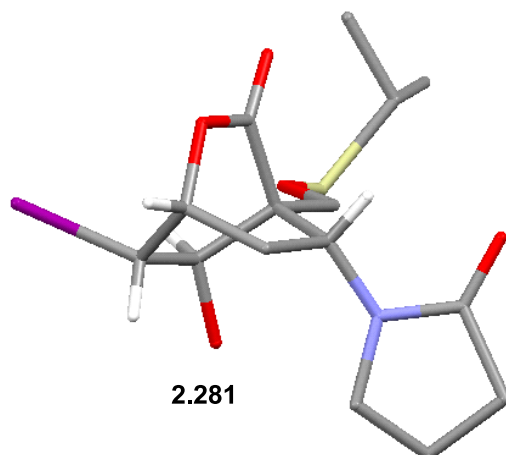


Figure 2.15: X-ray crystal structure of **2.281**.



A variety of hydride, amide, amine, and carbonate bases were screened to form the epoxide **2.282** from the iodohydrin **2.281** (Scheme 2.84). In general, we found that there was simply no reaction with all bases in THF but when DMF was used, we observed some consumption of the starting material, although, no epoxide was isolated. When acetonitrile was used in combination with NaOtBu or CsCO₃, we were able to isolate the desired *endo*-epoxide **2.282** in 52% and 70% yield, respectively. Epoxide

2.282 was found to be water sensitive, so the reaction was concentrated and chromatographed without aqueous workup. The structure of **2.282** was confirmed by X-ray crystallography (Figure 2.16).

Scheme 2.84: Successful epoxide formation from the iodohydrin

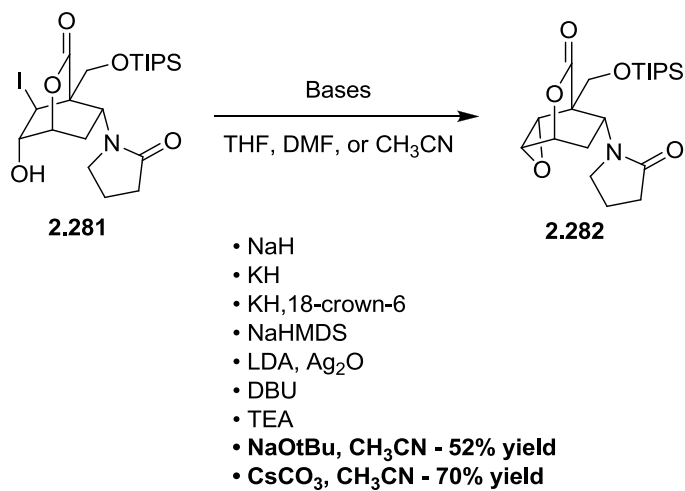
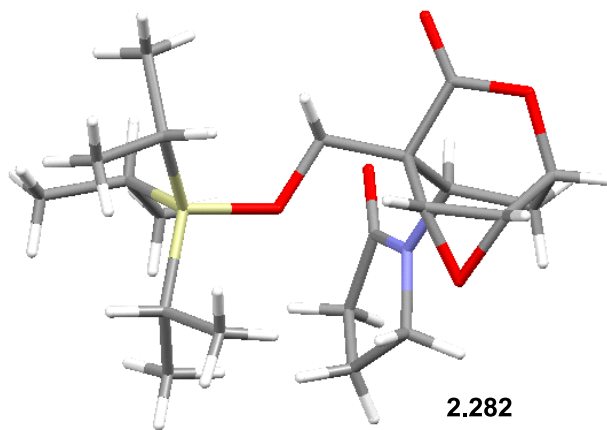
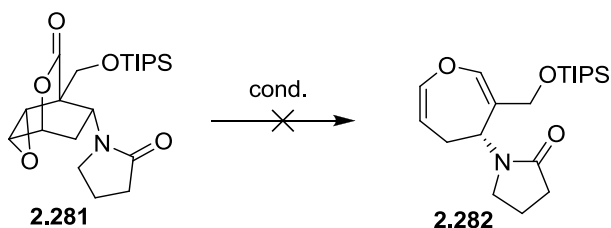


Figure 2.16: X-ray crystal structure of epoxide **2.282**.



We then screened a variety of conditions to induce the retro-homo Diels-Alder reaction of **2.282** (Scheme 2.85). Heating **2.281** in toluene, tetraglyme, hexafluoroisopropanol gave only recovered starting material, even at temperatures as high as 330 °C. No change was observed under microwave heating in toluene at 200 °C. Heating **2.282** under vacuum to encourage the extrusion of carbon dioxide gas also resulted in only recovered starting material. Exposure of **2.281** to Lewis acids TMSOTf, ZnBr₂, and Ti(OiPr)₄ led only to recovered **2.282**; no trace of desired oxepin **2.282** was detected. The failure of **2.281** to undergo the retro-homo Diels-Alder reaction may be due to the higher activation energy for the extrusion of carbon dioxide versus dinitrogen.^{149,172}

Scheme 2.85: Failed conditions for the retro-homo Diels-Alder reaction



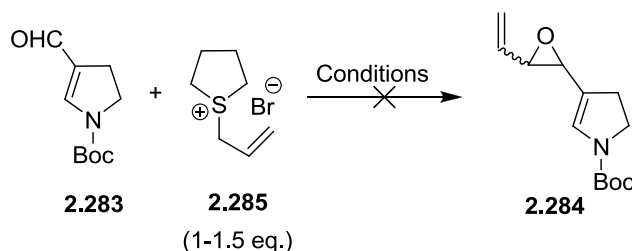
Conditions:

- toluene, 200 °C
- toluene, 200 °C, μ W
- tetraglyme, 330 °C
- HFIPA, 150 °C
- 200 °C, hi-vac
- BF₃OEt₂, DCE, 80 °C
- TMSOTf, DCE, 80 °C
- ZnBr₂, DCE, 150 °C
- Ti(OiPr)₄, DCE, 200 °C, μ W

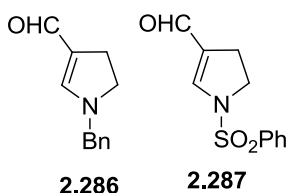
2.3.2.2. Cope rearrangement of divinyl epoxides

In order to explore the possibility of inducing the ring expansion of divinyl epoxides, we tried to convert the vinylogous formamide **2.283** into epoxide **2.284** (Scheme 2.86). Unsaturated aldehyde **2.283** was available in four steps from commercially available pyrrolidinone according to literature reports.^{206,207} Initial efforts focused on the use of the preformed sulfonium salt **2.285** to transform aldehyde **2.283** into vinyl substituted epoxide **2.284**.¹⁷⁸ A variety of bases^{179,180} and solvents¹⁸¹ were screened, but no conditions were identified that produced detectable amounts of desired epoxide **2.284**. Instead, we observed a slow decomposition of sulfoxonium salt **2.285** along with recovered aldehyde **2.283**. The *N*-Boc protecting group was exchanged with an *N*-benzyl group and an *N*-sulfonyl group and the substrates **2.286** and **2.287** were re-submitted to the reaction conditions, all of which failed to generate the epoxide.

Scheme 2.86: Failed attempts to form epoxide **2.284**.

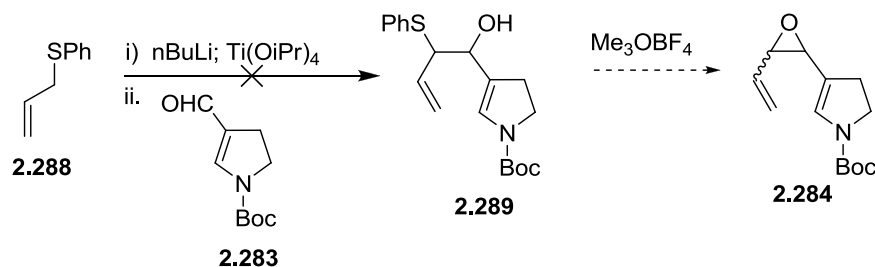


also tried:



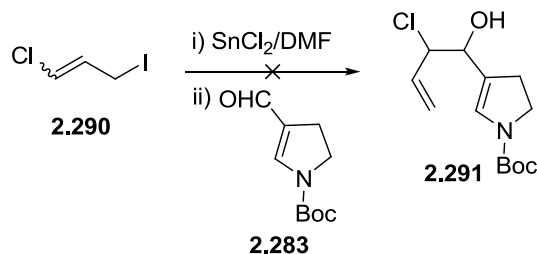
We also investigated the use of an organo-titanate nucleophile derived from the anion of phenyl allyl sulfide (**2.288**) to generate the alcohol **2.289** without success (Scheme 2.87).

Scheme 2.87: Attempted use of organo-titanate nucleophiles to form alcohol **2.286**.



In another unsuccessful attempt to generate a precursor of the epoxide **2.284**, chloro-iodopropene **2.290** was premixed with tin chloride prior to the addition of aldehyde **2.283** (Scheme 2.88).¹⁸²

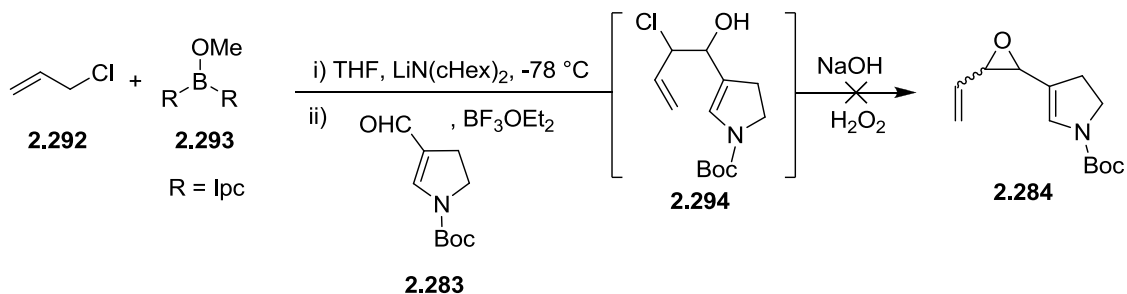
Scheme 2.88: Attempted tin promoted addition of allyl chloride



A Brown-type allylation of and aldehyde **2.283** was also briefly examined using a vinyl-borane generated from the anion of allylchloride (**2.292**),¹⁸⁶ but no trace of the

chlorohydrin **2.294** or epoxide **2.284** was detected (Scheme 2.89). Aldehydes **2.286** and **2.287** also failed to give any desired epoxide under the reaction conditions.

Scheme 2.89: Modified Brown-allylation of allylation of aldehyde **2.283**.



2.3.2.3. Summary and Conclusions

Our unsuccessful attempts to construct dihydrooxepins by the retro-homo Diels-Alder cycloaddition (Scheme 2.85) or by the Cope rearrangement of divinyl epoxides (Scheme 2.33) highlights the difficulties associated with the synthesis of this structural motif. Despite the failure to form dihydrooxepin **2.282** by loss of carbon dioxide, we speculate that perhaps the route can be redesigned to be more reactive through extrusion of nitrogen gas¹⁴⁹ or a nitroso group.¹⁵⁰ Our explorations into this route led to the development of epoxidation conditions for electronically deactivated olefins, which may be useful to future work toward this methodology (Scheme 2.84).

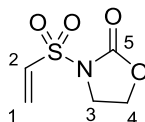
We were unable to attempt the Cope-rearrangement of divinyl epoxides due to the failure to generate epoxides from aldehydes **2.283**, **2.286** and **2.287**. These difficulties

may be due to the vinylogous nature of the formamide, which is not preceded to undergo nucleophilic additions from allyl anion equivalents. The route will need to be redesigned to avoid this transformation. If epoxides such as **2.284** could be easily accessed by alternative methods, Cope-rearrangement may serve as a rapid means for the construction of dihydrooxepine cores such as **2.176**.

Chapter 3: Experimental Section

General Methods: Nuclear magnetic resonance spectra were recorded on a 600, 500 or 400 MHz spectrometer. Chemical shifts are reported in parts per million (δ) and are referenced to the indicated deuterated solvent. Coupling constants (J) are reported in Hertz (Hz) and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; dt, doublet of triplets; ddd, doublet of doublets of doublets; dtd, doublet of triplets of doublets; dq, doublet of quartets; m, multiplet; comp, overlapping multiplets of non-magnetically equivalent protons; br, broad. Infrared (IR) spectra were obtained with a Nicolet IR100 FT-IR spectrometer, either neat on sodium chloride or as solutions in the solvent indicated. Band positions are given in reciprocal centimeters (cm^{-1}). Melting points were determined using a Thomas-Hoover Uni-melt capillary melting point apparatus and are uncorrected. All optical rotations were taken on an Atago AP-300 automatic polarimeter. Thin layer chromatography (TLC) was performed on glass-backed precoated silica gel plates (0.25 mm thick with 60 F₂₅₄) and were visualized using one or both of the following manners: UV light (254 nm) and staining with basic aqueous KMnO₄ or *p*-anisaldehyde. Column chromatography was performed using glass columns and “medium pressure” silica gel (Sorbent Technologies, 45-70 μ). Tetrahydrofuran and diethyl ether were dried by filtration through two columns of activated, neutral alumina according to the procedure described by Grubbs (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J., *Organometallics* **1996**, *15*, 1518-1520). Toluene was additionally deoxygenated by passing through activated Q5. Triethylamine, pyridine, dichloromethane, 2,6-di-*tert*-butylpyridine, and TBSOTf, TMSOTf were

distilled from CaH₂ prior to use. Furans were distilled from KOH immediately prior to use. All reagents were purchased and used as received unless otherwise stated. Glassware used in the reactions was dried overnight in an oven at 120 °C. All reactions were performed under an atmosphere of argon unless otherwise noted. Our thanks to Richard Pederson and Materia for graciously providing all metathesis catalysts for this work.



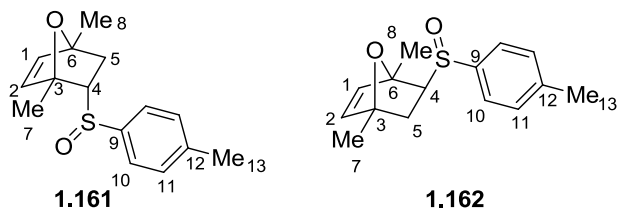
1.333

3-(Vinylsulfonyl)oxazolidin-2-one (1.133) (nb-2-164). A solution of 2-oxazolidinone (**1.136**) (1.94 g, 22.31 mmol) and Et₃N (12.44 mL, 89.24 mmol) in dry CH₂Cl₂ (200 mL) was cooled to -30 °C (dry-ice/acetone bath), and to this solution was added 2-chloroethanesulfonyl chloride (**1.137**) (4.00 g, 24.54 mmol, 2.56 mL) dropwise over 45 min with stirring. After the addition was completed, the mixture was stirred for 1.5 h at -30 °C. After this time, the reaction became cloudy and slightly orange in color. H₂O (100 mL) was added, and the mixture was extracted with CH₂Cl₂ (4 x 100 mL). The combined organics were washed with brine (1 x 100 mL) and dried (MgSO₄), filtered, and concentrated under reduced pressure to give 1.91 g of crude **1.333**, which was recrystallized from EtOAc/hex to provide 2.37 g (55%) of **1.333** as white crystals: mp 82-84 °C; ¹H NMR for **1.333** (500 MHz, CDCl₃) δ 6.85 (dd, *J* = 16.56, 9.90 Hz, 1H), 6.55 (dd, *J* = 16.6, 0.6 Hz, 1H), 6.24 (dd, *J* = 9.9, 0.7 Hz, 1H), 4.49-4.40 (AA'BB', *J* = 7.66, 7.91, 2H), 4.03 (AA'BB', *J* = 7.91, 7.65, 2H); ¹³C NMR for **1.333** (125 MHz, CDCl₃) δ

152.3, 131.4, 132.8, 62.7, 44.5; IR (neat) 1162.9, 1778.0; Mass Spectrum (CI) m/z 178.0172 [$C_5H_8NO_4S$ (M+1) requires 178.0174], 178 (base), 355.

NMR ASSIGNMENTS FOR 3-(Vinylsulfonyl)oxazolidin-2-one (**1.133**):

1H NMR for **1.333** (500 MHz, $CDCl_3$) δ 6.85 (dd, $J = 16.6, 9.9$ Hz, 1H, C2-H), 6.55 (dd, $J = 16.6, 0.6$ Hz, 1H, C1-H), 6.24 (dd, $J = 9.9, 0.7$ Hz, 1H, C1-H), 4.49-4.40 (AA'BB', 2H, C4-H), 4.03 (AA'BB', 2H, C3-H); ^{13}C NMR for **1.333** (125 MHz, $CDCl_3$) δ 152.3 (C5), 131.4 (C2), 132.8 (C1), 62.7 (C4), 44.5 (C3)



Procedure for the Asymmetric Diels-Alder Reaction with 2,5-dimethylfuran to furnish 1.161 and 1.162 (nb-2-155). To a solution of the sulfonium salt **1.82** (20 mg, 0.06 mmol) in anhydrous CH_2Cl_2 (200 μ L) was added 2,5-dimethylfuran (29 mg, 0.29 mmol, 31 μ L) *via* syringe at -78 $^{\circ}C$. The reaction mixture was stirred at -78 $^{\circ}C$ for 1 h then placed in a -20 $^{\circ}C$ refrigerator for 11 h. KOH (0.2 M, 0.5 mL) was added to the solution and the reaction mixture was warmed to room temperature, with stirring for an additional 30 min at room temperature. The reaction mixture was extracted with CH_2Cl_2 (3 x 2 mL), washed with brine (4 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield a mixture of **1.161** and **1.162** as white crystals (19 mg, 95%, endo/exo =

1:0.18, endo d.e. = 90%, exo d.e. = 84%, established by ^1H NMR). Crude material purified by reverse phase HPLC using a semi-prep gemini 10 μ C18 column, 0-95% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ increasing gradient over 60 min, 10 mL/min flow rate. ^1H NMR for **1.161** (500 MHz, CDCl_3) δ 7.61 – 7.47 (comp, 2 H), 7.26 (dd, J = 8.5, 0.6 Hz, 2 H), 6.50 (d, J = 5.6 Hz, 1 H), 6.33 (d, J = 5.6 Hz, 1 H), 3.19 (dd, J = 8.8 Hz, 3.9 1 H), 2.38 (s, 3 H), 1.81 (s, 3 H), 1.61 (dd, J = 12.2, 9.0 Hz, 1 H), 1.51 (s, 3 H), 1.15 (dd, J = 12.3, 3.9 Hz, 1 H); ^{13}C NMR for **1.161** (125 MHz, CDCl_3) δ 142.25, 140.88, 140.74, 136.82, 130.2, 125.3, 88.6, 85.6, 71.3, 36.2, 21.6, 19.9, 18.8; MS (CI) m/z 263.1109 [$\text{C}_{15}\text{H}_{19}\text{O}_2\text{S}$ (M+1) requires 263.1106], 263 (base), 267.

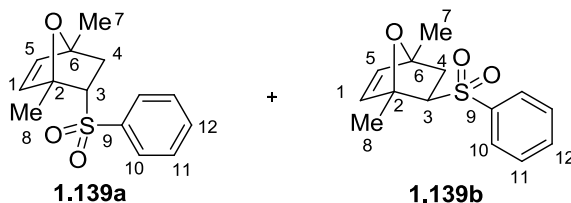
^1H NMR for **1.162** (500 MHz, CDCl_3) δ 7.65 – 7.54 (comp, 2 H), 7.27 (d, J = 7.8 Hz, 2 H), 6.19 (d, J = 5.5 Hz, 1 H), 6.13 (d, J = 5.5 Hz, 1 H), 2.88 (dd, J = 8.0, 4.6 Hz, 1 H), 2.38 (s, 3 H), 1.93 (s, 3 H), 1.52 (s, 3 H), 1.27 (dd, J = 12.5, 8.0 Hz, 1 H), 1.07 (dd, J = 12.5, 4.6 Hz, 1 H); ^{13}C NMR for **1.162** (125 MHz, CDCl_3) δ 142.40, 140.83, 140.48, 139.25, 130.09, 126.14, 87.92, 85.46, 70.91, 37.76, 21.68, 18.65, 17.62; MS (CI) m/z 263.1110 [$\text{C}_{15}\text{H}_{19}\text{O}_2\text{S}$ (M+1) requires 263.1106], 263 (base).

NMR ASSIGNMENTS FOR 1.161:

^1H NMR for **1.161** (500 MHz, CDCl_3) δ 7.61 – 7.47 (comp, 2 H, C10-H), 7.26 (dd, J = 8.5, 0.6 Hz, 2 H, C11-H), 6.50 (d, J = 5.6 Hz, 1 H, C2-H), 6.33 (d, J = 5.6 Hz, 1 H, C1-H), 3.19 (dd, J = 8.8, 3.9 Hz, 1 H, C4-H), 2.38 (s, 3 H, C13-H), 1.81 (s, 3 H, C7-H), 1.61 (dd, J = 12.2 9.0 Hz, 1 H, C5-H endo), 1.51 (s, 3 H, C8-H), 1.15 (dd, J = 12.3, 3.9 Hz, 1H, C5-H exo); ^{13}C NMR for **1.161** (125 MHz, CDCl_3) δ 142.25 (C9), 140.88(C12), 140.74(C1), 136.82(C2), 130.2(C11), 125.3(C10), 88.6(C3), 85.6(C6), 71.3(C4), 36.2(C5), 21.6(C13), 19.9(C7), 18.8(C8).

NMR ASSIGNMENTS FOR **1.162**:

^1H NMR for **1.162** (500 MHz, CDCl_3) δ 7.65 – 7.54 (comp, 2 H, C10-H), 7.27 (d, $J = 7.8$ Hz, 2 H, C11-H), 6.19 (d, $J = 5.5$ Hz, 1 H, C1-H), 6.13 (d, $J = 5.5$ Hz, 1 H, C2-H), 2.88 (dd, $J = 8.0, 4.6$ Hz, 1 H, C4-H), 2.38 (s, 3 H, C13-H), 1.93 (s, 3 H, C8-H), 1.52 (s, 3 H, C7-H), 1.27 (dd, $J = 12.5, 8.0$ Hz, 1 H, C5-H endo), 1.07 (dd, $J = 12.5, 4.6$ Hz, 1 H, C5-H exo); ^{13}C NMR for **1.162** (125 MHz, CDCl_3) δ 142.4 (C9), 140.8 (C12), 140.5 (C2), 139.3 (C1), 130.1 (C11), 126.1 (C10), 87.9 (C6), 85.5 (C3), 70.9 (C4), 37.8 (C5), 21.7 (C13), 18.7 (C7), 17.6 (C8)

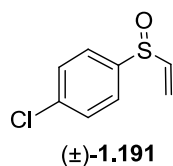


Procedure for AlMe_3 mediated the Diels-Alder Reaction with 2,5-dimethylfuran to furnish **1.139a and **1.139b** (nb-2-69).** AlMe_3 (2 M in hexane) (120 μL , 0.238 mmol) was added dropwise to a dry, argon-purged, vial containing vinyl sulfone **1.126** (20 mg, 0.119 mmol) in CH_2Cl_2 (200 μL) with stirring at 0°C . The solution was stirred for 20 min at 0°C , and 2,5-dimethylfuran (freshly distilled from KOH) (57.2 mg, 63 μL , 0.595 mmol) was added dropwise over 1 min with rapid stirring. The reaction was then stirred at 5°C (refrigerator) for 36 h. The reaction was allowed to warm to 25°C before filtration through a short plug of silica with CH_2Cl_2 (12 mL). The

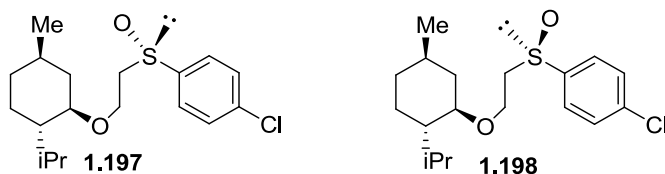
filtrate was then concentration by rotary evaporation to yield 35 mg of pale yellow oil. The crude material was purified via column chromatography eluting with Et₂O/Pentane (2:3) to provide 26 mg of **1.139a** (top spot) and 3 mg of **1.139b** (lower spot) (95%), both as white crystals. ¹H NMR for **1.139a** (500 MHz, CDCl₃) δ 7.89-7.82 (comp, 2 H), 7.69-7.61 (m, 1 H), 7.59-7.52 (comp, 2 H), 6.38-6.30 (comp, 2 H), 3.54 (dd, *J* = 8.9, 4.5 Hz, 1 H), 1.98 (dd, *J* = 11.8, 8.9 Hz, 1 H), 1.91 (dd, *J* = 11.8, 4.5 Hz, 1 H), 1.69 (s, 3 H), 1.57 (s, 3 H); ¹³C NMR for **1.139a** (125 MHz, CDCl₃) δ 140.7, 140.2, 135.7, 133.6, 129.3, 127.9, 87.6, 86.2, 69.9, 38.5, 19.0, 18.6; IR (neat) 1147.9, 2931.3; MS (CI) *m/z* 265.0895 [C₁₄H₁₇O₃S (M+1) requires 263.0898], 169, 265 (base), 377.

NMR ASSIGNMENTS FOR **1.139a**:

¹H NMR for **1.139a** (500 MHz, CDCl₃) δ 7.89-7.82 (comp, 2 H, C10-H), 7.69-7.61 (comp, 1 H, C12-H), 7.59-7.52 (comp, 2 H, C11-H), 6.38-6.30 (app.s, ab pattern, 2 H, C1-H, C5-H), 3.54 (dd, *J* = 8.9, 4.5 Hz, 1 H, C3-H), 1.98 (dd, *J* = 11.8, 8.9 Hz, 1 H, C4-H), 1.91 (dd, *J* = 11.8, 4.5 Hz, 1 H, C5-H), 1.69 (s, 3 H, C8-H), 1.57 (s, 3 H, C7-H); ¹³C NMR for **1.140** (125 MHz, CDCl₃) δ 140.7 (C9), 140.2 (C1), 135.7 (C5), 133.6 (C12), 129.3 (C11), 127.9 (C10), 87.6 (C2), 86.2 (C6), 69.9 (C3), 38.5 (C4), 19.0 (C8), 18.6 (C7).



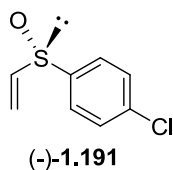
1-Chloro-4-(vinylsulfinyl)benzene (1.191) (nb-3-60). 4-Chlorophenyl vinyl sulfide (10.14 g, 170.66 mmol) was dissolved in AcOH (20 mL) and cooled to 0 °C, and H₂O₂ (30% aq.) (8.42 g, 8.42 mL, 34.01 mmol) was added dropwise with rapid stirring. The reaction was stirred at 0 °C for 1 h after which time the solution was warmed to room temperature and stirred for 12 h. The now homogenous solution was diluted with H₂O (30 mL) and extracted with Et₂O (3 x 30 mL). To the combined organics was added solid NaHCO₃ followed by saturated aqueous NaHCO₃ (ca. 15 mL) until all of the acid was neutralized. The organic layer was then separated and dried (MgSO₄), filtered, and concentrated by rotary evaporation. The crude oil was then purified by flash chromatography (1:1 EtOAc/Hex to 2:1 EtOAc/Hex) to yield the product **1.191** (10.07 g, 91%) as a pale yellow oil. The ¹H and ¹³C NMR spectra were consistent with those reported in the literature.^{208,209}



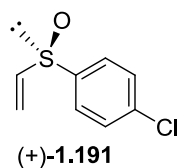
1-Chloro-4-(2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)ethylsulfinyl)benzene (1.197, 1.198) (nb-2-290). (-)-Menthol (1.09 g, 6.96 mmol) in THF (3 mL) was added to a suspension of NaH (60% dispersion in mineral oil) (278 mg, 6.96 mmol) in THF (9 mL) at rt. The suspension was stirred for 30 min. and vinyl sulfoxide **1.191** (1 g, 5.36 mmol) in THF (3 mL) was added, immediately followed by a catalytic amount of KH. Upon addition of KH, the reaction became brown in color. The reaction was stirred for 4 h until all starting material was consumed by TLC. The reaction was quenched by dilution with Et₂O (15 mL) followed by the slow addition of brine until all bubbling had ceased. The mixture was extracted with Et₂O (3 x 15 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography (15% EtOAc/Hex to 30% EtOAc/Hex) to yield **1.197** and **1.198** (1.50 g, 81% yield) as a mixture (1:1) of diastereomers as a yellow oil. This mixture was then dissolved in Et₂O and cooled to 5 °C, whereupon **1.197** crystallized as x-ray quality white spikes (mp 102-105 °C). The mother liquor was diluted with pentane and cooled to -20 °C overnight, resulting in a second crop of **1.197** (741 mg total, 40% yield, >95% de by NMR). The mother liquor was then concentrated under reduced pressure and purified by column chromatography (15% EtOAc/Hex to 30% EtOAc/Hex) to yield **1.198** (609 mg, 33% yield, >95% de by NMR) as an off-white solid. ¹H NMR for **1.197** (500 MHz, CDCl₃) δ 7.60-7.59 (comp, 2 H), 7.51-7.49 (comp, 2 H), 4.09-4.06 (m, 1 H), 3.60-3.56 (m, 1 H), 3.09-3.05 (m, 1 H), 2.98-2.95 (m, 2 H), 2.16-2.12 (m, 2 H), 1.66-1.61 (m, 2 H), 1.38-1.31 (m, 1 H), 1.26-1.20

(m, 1 H), 0.99-0.82 (m, 9 H), 0.76 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR for **1.197** (125 MHz, CDCl_3) δ 143.0, 137.1, 129.5, 125.4, 79.8, 61.1, 59.2, 48.1, 40.2, 34.4, 31.5, 25.6, 23.3, 22.2, 20.9, 16.3; IR (neat) 2953, 1475, 1051 cm^{-1} ; HRMS (CI) m/z calculated for $\text{C}_{18}\text{H}_{28}\text{O}_2\text{SCl}$ (M+1) 343.1499; found, 343.1504; mass spectrum, 326, 343 (base), 345.

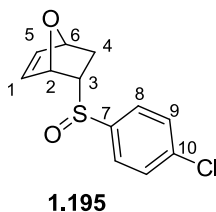
^1H NMR for **1.198** (500 MHz, CDCl_3) δ 7.62-7.57 (comp, 2 H), 7.52-7.48 (comp, 2 H), 3.96-3.86 (m, 1 H), 3.76 (ddd, $J = 10.4, 9.3, 4.2$ Hz, 1 H), 3.16 (dt, $J = 10.6, 4.2$ Hz, 1 H), 2.95 (comp., 2 H), 2.27 (dtd, $J = 13.95, 6.96, 2.77$ Hz, 1 H), 2.08 (comp, 2 H), 1.65 (comp, 2 H), 1.45-1.30 (m, 1 H), 1.23 (tdd, $J = 13.38, 10.35, 3.18$ Hz, 1 H), 1.06-0.95 (m, 1 H), 0.95-0.89 (dd, $J = 6.6, 3.6$ Hz, 6 H), 0.84 (comp., 5 H); ^{13}C NMR for **1.198** (125 MHz, CDCl_3) δ 143.1, 137.0, 129.5, 125.3, 80.2, 60.8, 59.4, 48.3, 40.2, 34.5, 31.4, 25.7, 23.3, 22.3, 20.9, 16.3; ; IR (neat) 2953, 1475, 1091 cm^{-1} ; ; HRMS (CI) m/z calculated for $\text{C}_{18}\text{H}_{28}\text{O}_2\text{SCl}$ (M+1) 343.1499; found, 343.1497; mass spectrum, 331, 343 (base), 380.



(-)-1-Chloro-4-(vinylsulfinyl)benzene ((-)-1.191) (nb-3-53). A solution of LiHMDS (1M in THF) (1.63 g, 1.83 mL, 1.823 mmol) was added to a solution of diastereomerically pure sulfoxide **1.197** (500 mg, 1.458 mmol) in THF (10 mL) at -78 °C. The reaction was stirred for 45 sec. after which time it was quenched by the rapid addition of NH₄Cl (sat. aq. soln.) and then allowed to warm to room temp. The mixture was then extracted with CH₂Cl₂ (3 x 10 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude oil was purified by column chromatography (30% EtOAc/Hex) to yield **(-)-1.191** (171 mg, 61% yield) as a pale yellow oil. The ¹H and ¹³C NMR spectra were consistent with those reported in the literature.²⁰⁸ The purified **(-)-1.191** was separated via HPLC on a Chiral OB column in >99% *ee* (1 mL/min, 0% to 30% iPrOH/hexanes gradient over 30 min) in >99% *ee*, the two enantiomers eluting at 21.24 min. and the minor at 25.32 min.; [α]_D²⁷ -345° (*c* 0.2, CH₂Cl₂).



(+)-1-Chloro-4-(vinylsulfinyl)benzene ((+)-1.191) (nb-3-51). A solution of LiHMDS (1M in THF) (1.63 g, 1.83 mL, 1.823 mmol) was added to a solution of diastereomerically pure sulfoxide **1.198** (500 mg, 1.458 mmol) in THF (10 mL) at -78 °C. The reaction was stirred for 45 sec. after which time it was quenched by the rapid addition of NH₄Cl (sat. aq. soln.) and then allowed to warm to room temp. The mixture was then extracted with CH₂Cl₂ (3 x 10 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude oil was purified by column chromatography (30% EtOAc/Hex) to yield **(+)-1.191** (185 mg, 66% yield) as a pale yellow oil. The ¹H and ¹³C NMR spectra were consistent with those reported in the literature.²⁰⁸ The purified **(+)-1.191** was separated *via* HPLC on a Chiral OB column (1 mL/min, 0% to 30% iPrOH/hexanes gradient over 30 min) in >99% *ee*, the two enantiomers eluting at 21.24 min. and the major at 25.32 min.; [α]_D²⁷ +338° (*c* 0.2, CH₂Cl₂).



(1S,2S,4S)-2-(4-Chlorophenylsulfinyl)-7-oxabicyclo[2.2.1]hept-5-ene (1.195)

(nb-4-58). TBSOTf (123 μ L, 0.536 mmol) was added dropwise to a solution of *p*-chlorophenyl-vinylsulfoxide **(-)-1.191** (100 mg, 0.54 mmol) and 2,6-di-tert-butylpyridine (12 μ L, 0.06 mmol) in CH₃CN (200 μ L) at 0 °C. The mixture was stirred for 15 min, whereupon furan (364 mg, 195 μ L, 2.68 mmol) was added dropwise. The reaction was stored for 24 h at 0 °C (refrigerator). Saturated aqueous NaHCO₃ (1 mL) was then added, and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL), and the combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (66% to 100%) to give 137.5 mg (99%) of **1.195** as a mixture of *endo:exo* isomers (1.8:1) and as a clear oil. **Endo-1.195** was separated via HPLC using a Chiral OB column (1 mL/min, 0% to 30% iPrOH/hexanes over 30 min) with the two diastereomers eluting at 28.28 min and 40.85 min in 90% de. **Exo-1.195** was separated via HPLC using a Chiral OB column (1 mL/min, 0% to 30% iPrOH/hexanes over 30 min) with the two enantiomers eluting at 30.35 min and 35.30 min in 88% ee. The product major *endo* isomer was recrystallized via slow evaporation from Et₂O to give X-ray quality crystals (mp: 104-105 °C); ¹H NMR for **endo-1.195** (400 MHz, CDCl₃) δ 7.63-7.56 (comp, 2 H), 7.56-7.51 (comp, 2 H), 6.58 (dd, *J* = 5.9, 1.7 Hz, 1 H), 6.37 (dd, *J* = 5.9, 1.5 Hz, 1 H), 5.12-5.06 (m, 1 H), 4.75 (ddd, *J* = 4.2, 1.5, 0.7 Hz, 1 H), 3.42-3.35 (m, 1 H), 2.13 (ddd, *J* = 13.3, 8.5, 4.3 Hz, 1 H), 1.79 (dd, *J* = 12.3, 3.8 Hz, 1 H); ¹³C NMR for **endo-1.195** (125

MHz, CDCl₃) δ 142.5, 137.9, 137.6, 131.1, 129.8, 125.5, 79.1, 78.2, 64.9, 25.9; IR (neat) 3011, 1045; HRMS (CI) m/z calculated for C₁₂H₁₂O₂SCl⁺ (M+1), 255.0247; found, 255.0243; mass spectrum, 237 (base), 239, 268.

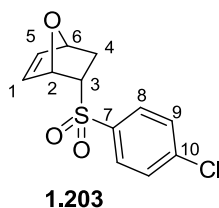
¹H NMR for **exo-1.195** (400 MHz, CDCl₃) δ 7.68-7.61 (comp, 2 H), 7.55-7.49 (comp, 2 H), 6.45 (dd, J = 5.8, 1.6 Hz, 1 H), 6.24 (dd, J = 5.8, 1.8 Hz, 1 H), 5.16-5.10 (m, 1 H), 4.96 (dd, J = 1.8, 0.7 Hz, 1 H), 2.75 (dd, J = 7.9, 3.6 Hz, 1 H), 2.29 (app. dt, J = 12.3, 4.0, 1 H), 1.56 (dd, J = 12.4, 7.9 Hz, 1 H); ¹³C NMR for **exo-1.195** (100 MHz, CDCl₃) δ 141.9, 138.4, 137.7, 133.6, 129.7, 126.2, 79.0, 78.5, 64.7, 26.7; IR (neat) 3009, 1046; HRMS (CI) m/z calculated for C₁₂H₁₂O₂SCl⁺ (M+1), 255.0247; found, 255.0247; mass spectrum, 237 (base), 269.

NMR ASSIGNMENTS FOR **endo-1.195**:

¹H NMR for **endo-1.195** (400 MHz, CDCl₃) δ 7.63-7.56 (comp, 2 H, C8-H), 7.56-7.51 (comp, 2 H, C9-H), 6.58 (dd, J = 5.9, 1.7 Hz, 1 H, C1-H), 6.37 (dd, J = 5.9, 1.5 Hz, 1 H, C5-H), 5.12-5.06 (m, 1 H, C2-H), 4.75 (ddd, J = 4.2, 1.5, 0.7 Hz, 1 H, C6-H), 3.42-3.35 (m, 1 H, C3-H), 2.13 (ddd, J = 13.3, 8.5, 4.3 Hz, 1 H, C4-H), 1.79 (dd, J = 12.3, 3.8 Hz, 1 H, C4-H); ¹³C NMR for **endo-1.195** (100 MHz, CDCl₃) δ 142.5 (C7), 137.9 (C1), 137.6 (C10), 131.1 (C5), 129.8 (C9), 125.5 (C8), 79.1 (C6), 78.2 (C2), 64.9 (C3), 25.9 (C4).

NMR ASSIGNMENTS FOR *exo*-1.195:

^1H NMR for *exo*-1.195 (400 MHz, CDCl_3) δ 7.68-7.61 (comp, 2 H, C8-H), 7.55-7.49 (comp, 2 H, C9-H), 6.45 (dd, $J = 5.8, 1.6$ Hz, 1 H, C1-H), 6.24 (dd, $J = 5.8, 1.8$ Hz, 1 H, C5-H), 5.16-5.10 (m, 1 H, C2-H), 4.96 (dd, $J = 1.8, 0.7$ Hz, 1 H, C6-H), 2.75 (dd, $J = 7.9, 3.6$ Hz, 1 H, C3-H), 2.29 (app. dt, $J = 12.3, 4.0$, 1 H, C4-H), 1.56 (dd, $J = 12.4, 7.9$ Hz, 1 H, C4-H); ^{13}C NMR for *exo*-1.195 (100 MHz, CDCl_3) δ 141.9 (C7), 138.4 (C1), 137.7 (C10), 133.6 (C5), 129.7 (C9), 126.2 (C8), 79.0 (C6), 78.5 (C2), 64.7 (C3), 26.7 (C4).



(1S,2S,4S)-2-(4-chlorophenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene (1.203) (nb-4-48). TBSOTf (123 μL , 0.536 mmol) was added dropwise to a solution of *p*-chlorophenyl-vinylsulfoxide (-)-1.191 (100 mg, 0.54 mmol) and 2,6-di-*tert*-butylpyridine (12 μL , 0.06 mmol) in CH_3CN (200 μL) at 0 $^\circ\text{C}$. The mixture was stirred for 15 min, whereupon furan (195 μL , 2.68 mmol) was added dropwise. The reaction was stored for 24 h at 0 $^\circ\text{C}$ (refrigerator), whereupon 20% TEA in MeOH (500 μL) was added followed by Oxone (600 mg, 1.95 mmol). The suspension was stirred for 6 h and H_2O (4 mL) was added. The mixture was extracted with Et_2O (4 x 5 mL), and the combined organic layers were dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (25% to 50%) to give

143.5 mg (98%) of **1.203** as a (1.8:1) mixture of *endo:exo* isomers and as a white solid: **endo-1.203** mp: 151-152 °C (clear needles by slow evaporation from Et₂O), **exo-1.203** mp: 138-140 °C (white needles by slow evaporation from Et₂O); **endo-1.203** was separated via HPLC using a Chiral AD column (1 mL/min, 0% to 30% iPrOH/hexanes over 15 min) with the two enantiomers eluting at 30.73 min and 40.76 min in 88% ee; The **endo-1.203** was recrystallized by slow evaporation from Et₂O to give X-ray crystal **77**; ¹H NMR for **endo-1.203** (400 MHz, CDCl₃) δ 7.86-7.75 (comp, 2 H), 7.61-7.51 (comp, 2 H), 6.58 (dd, *J* = 5.6, 1.5 Hz, 1 H), 6.48 (dd, *J* = 5.8, 1.5 Hz, 1 H), 5.18-5.02 (comp., 2 H), 3.76-3.64 (app. pent, *J* = 4.4 Hz, 1 H), 2.19 (ddd, *J* = 17.6, 9.1, 4.8, 1 H), 1.67 (dd, *J* = 11.7, 4.5 Hz, 1 H); ¹³C NMR for **endo-1.203** (125 MHz, CDCl₃) δ 140.6, 138.9, 137.5, 131.6, 129.8, 129.3, 79.6, 78.3, 62.8, 28.8; IR (neat) 1310, 1149 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₂H₁₂O₃SCl⁺ (M+1), 271.0196; found, 271.0193; mass spectrum, 269, 271 (base), 273; [α]_D²⁷ -27.6° (*c* 0.2, CH₂Cl₂).

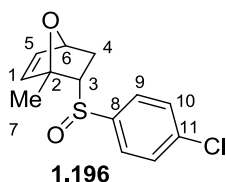
¹H NMR for **exo-1.203** (600 MHz, CDCl₃) δ 7.86-7.82 (comp, 2 H), 7.55-7.51 (comp, 2 H), 6.44 (dd, *J* = 5.8, 1.7 Hz, 1 H), 6.33 (dd, *J* = 5.8, 1.8 Hz, 1 H), 5.32 (dd, *J* = 1.8, 0.8 Hz, 1 H), 5.05 (ddd, *J* = 4.6, 1.5, 0.8 Hz, 1 H), 3.11 (dd, *J* = 8.2, 4.2 Hz, 1 H), 2.17-2.09 (m, 1 H), 1.64 (dd, *J* = 8.2, 12.3, 1 H); ¹³C NMR for **exo-1.203** (125 MHz, CDCl₃) δ 140.6, 138.5, 136.8, 134.2, 130.2, 129.6, 78.9, 78.1, 64.1, 28.1; IR (neat) 2921.1, 1311.9, 1149.3 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₂H₁₂O₃SCl⁺ (M+1), 271.0196; found, 271.0201; mass spectrum, 269, 271 (base); [α]_D²⁷ +17.3° (*c* 0.2, CH₂Cl₂).

NMR ASSIGNMENTS FOR *endo*-1.203:

^1H NMR for *endo*-1.203 (400 MHz, CDCl_3) δ 7.86-7.75 (comp, 2 H, C8-H), 7.61-7.51 (comp, 2 H, C9-H), 6.58 (dd, $J = 5.6, 1.5$ Hz, 1 H, C1-H), 6.48 (dd, $J = 5.8, 1.5$ Hz, 1 H, C5-H), 5.18-5.02 (comp, 2 H, C2-H and C6-H), 3.76-3.64 (app pent, $J = 4.4$ Hz, 1 H, C3-H), 2.19 (ddd, $J = 17.6, 9.1, 4.8$, 1 H, C4-H), 1.67 (dd, $J = 11.7, 4.5$ Hz, 1 H, C4-H); ^{13}C NMR for *endo*-1.203 (125 MHz, CDCl_3) δ 140.6 (C10), 138.9 (C7), 137.5 (C8), 131.6 (C9), 129.8 (C1), 129.3 (C2), 79.6 (C2), 78.3 (C6), 62.8 (C3), 28.8 (C4).

NMR ASSIGNMENTS FOR *exo*-1.203:

^1H NMR for *exo*-1.203 (600 MHz, CDCl_3) δ 7.86-7.82 (comp, 2 H, C8-H), 7.55-7.51 (comp, 2 H, C9-H), 6.44 (dd, $J = 5.8, 1.7$ Hz, 1 H, C1-H), 6.33 (dd, $J = 5.8, 1.8$ Hz, 1 H, C5-H), 5.32 (dd, $J = 1.8, 0.8$ Hz, 1 H, C2-H), 5.05 (ddd, $J = 4.6, 1.5, 0.8$ Hz, 1 H, C6-H), 3.11 (dd, $J = 8.2, 4.2$ Hz, 1 H, C3-H), 2.17-2.09 (m, 1 H, C4-H), 1.64 (dd, $J = 8.2, 12.3$, 1 H, C4-H); ^{13}C NMR for *exo*-1.203 (125 MHz, CDCl_3) δ 140.6 (C10), 138.5 (C8), 136.8 (C7), 134.2 (C9), 130.2 (C1), 129.6 (C5), 78.9 (C2), 78.1 (C6), 64.1 (C3), 28.1 (C4).



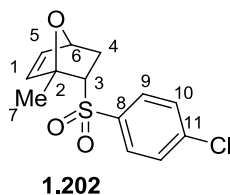
(1R,2S,4S)-2-(4-chlorophenylsulfinyl)-1-methyl-7-oxabicyclo[2.2.1]hept-5-ene

(1.196) (nb-4-101). TBSOTf (37 μ L, 0.16 mmol) was added dropwise to a solution of *p*-chlorophenyl-vinylsulfoxide **(-)-1.191** (40 mg, 0.21 mmol) and 2,6-di-*tert*-butylpyridine (3.4 mg, 4 μ L, 0.02 mmol) in CH₃CN (100 μ L) at -30 °C. The mixture was stirred for 15 min, whereupon 2-methylfuran (36.4 mg, 40 μ L, 0.43 mmol) was added dropwise. The reaction was stored for 24 h at -30 °C (freezer). Saturated aqueous NaHCO₃ (800 μ L) was then added with rapid stirring, and the mixture was allowed to warm to room temperature. CH₂Cl₂ (2 mL) was added, and the layers were separated. The aqueous layer was then extracted with CH₂Cl₂ (3 x 4 mL), and the combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (50% to 66%) to give 51 mg (89%) of **1.196** as a (25:1) mixture of *endo:exo* isomers and as a clear oil; **Endo-1.196** was separated via HPLC using a Chiral AD column (1 mL/min, 0% to 20% iPrOH/hexanes over 30 min) with the two diastereomers eluting at 28.09 min and 31.61 min in 99% de; The product **endo-1.196** was then recrystallized via slow evaporation from Et₂O to give X-ray quality crystals (mp: 76-78 °C); ¹H NMR for **endo-1.196** (600 MHz, CDCl₃) δ 7.55-7.41 (comp, 4 H), 6.48 (d, *J* = 5.7 Hz, 1 H), 6.18 (d, *J* = 5.6 Hz, 1 H), 4.94-4.86 (m, 1 H), 2.82 (dd, *J* = 8.6, 3.9 Hz, 1 H), 1.97-1.91 (m, 1 H) 1.83-1.75 (m, 1 H), 1.61 (s, 3 H); ¹³C NMR for **endo-1.196** (125 MHz, CDCl₃) δ 142.7, 137.9, 137.0, 134.0, 129.5, 125.3, 86.3, 78.3, 68.8, 26.6, 17.8; IR (neat) 2975, 1475, 1388 cm⁻¹; HRMS (CI) *m/z*

calculated for $C_{13}H_{14}O_2SCl^+$ (M+1), 269.0403; found, 271.0406; mass spectrum, 251 (base), 269; $[\alpha]_D^{21} +182.3^\circ$ (c 1.0, CH_2Cl_2).

NMR ASSIGNMENTS FOR *endo*-1.196:

1H NMR for *endo*-1.196 (600 MHz, $CDCl_3$) δ 7.55-7.41 (comp, 4 H, C9-H and C10-H), 6.48 (d, $J = 5.7$ Hz, 1 H, C1-H), 6.18 (d, $J = 5.6$ Hz, 1 H, C5-H), 4.94-4.86 (m, 1 H, C6-H), 2.82 (dd, $J = 8.6, 3.9$ Hz, 1 H, 3-H), 1.97-1.91 (m, 1 H, C4-H) 1.83-1.75 (m, 1 H, C4-H), 1.61 (s, 3 H, C7-H); ^{13}C NMR for *endo*-1.196 (125 MHz, $CDCl_3$) δ 142.7 (C8), 137.9 (C1), 137.0 (C11), 134.0 (C5), 129.5 (C10), 125.3 (C9), 86.3 (C2), 78.3 (C6), 68.8 (C3), 26.6 (C4), 17.8 (C7).

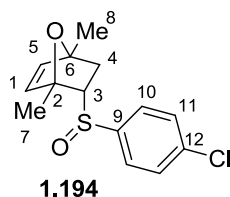


(1R,2S,4S)-2-(4-chlorophenylsulfonyl)-1-methyl-7-oxabicyclo[2.2.1]hept-5-ene (1.202) (nb-4-102). TBSOTf (37 μ L, 0.16 mmol) was added dropwise to a solution of *p*-chlorophenyl-vinylsulfoxide (-)-1.191 (40 mg, 0.21 mmol) and 2,6-di-*tert*-butylpyridine (3.4 mg, 4 μ L, 0.02 mmol) in CH_3CN (100 μ L) at $-30^\circ C$. The mixture was stirred for 15 min, whereupon 2-methylfuran (36.4 mg, 40 μ L, 0.43 mmol) was added dropwise. The reaction was stored for 24 h at $-30^\circ C$ (freezer), whereupon 20% TEA in MeOH (300 μ L) was added followed by Oxone (300 mg, 0.98 mmol). The suspension

was stirred for 6 h and H₂O (3 mL) was added. The mixture was extracted with Et₂O (4 x 3 mL) and the combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (10% to 30%) to give 48.4 mg (81%) of **1.202** as a mixture of *endo:exo* isomers (>25:1) as a white solid. **Endo-1.202** was separated via HPLC using a Chiral AD column (1 mL/min, 0% to 20% iPrOH/hexanes over 30 min) with the two enantiomers eluting at 28.62 min and 31.91 min in 99% ee; The major *endo* isomer was recrystallized from Et₂O/pentane: mp: 89-91 °C; ¹H NMR for **endo-1.202** (400 MHz, CDCl₃) δ 7.57-7.51 (comp, 2 H), 7.82-7.76 (comp, 2 H), 6.52 (dd, *J* = 5.7, 1.7 Hz, 1 H), 6.35 (d, *J* = 5.7 Hz, 1 H), 4.94 (dd, *J* = 4.7, 1.8 Hz, 1 H), 3.37 (dd, *J* = 9.1, 4.4 Hz, 1 H), 2.31-2.24 (m, 1 H), 1.77-1.71 (comp, 4 H); ¹³C NMR for **endo-1.202** (100 MHz, CDCl₃) δ 140.4, 139.1, 137.5, 135.1, 129.7, 129.4, 87.7, 78.2, 67.3, 32.5, 18.8; IR (neat) 3090, 1582, 1317 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₃H₁₄O₃SCl⁺ (M+1), 285.0352; found, 285.0352; mass spectrum, 269, 285 (base), 287; [α]_D²⁸ -20.4° (*c* 0.2, CH₂Cl₂).

NMR ASSIGNMENTS FOR **endo-1.202**:

¹H NMR for **endo-1.202** (400 MHz, CDCl₃) δ 7.57-7.51 (comp, 2 H, C9-H), 7.82-7.76 (comp, 2 H, C10-H), 6.52 (dd, *J* = 5.7, 1.7 Hz, 1 H, C1-H), 6.35 (d, *J* = 5.7 Hz, 1 H, C5-H), 4.94 (dd, *J* = 4.7, 1.8 Hz, 1 H, C6-H), 3.37 (dd, *J* = 9.1, 4.4 Hz, 1 H, C3-H), 2.31-2.24 (m, 1 H, C4-H), 1.77-1.71 (comp., 4 H, C4-H and C7-H); ¹³C NMR for **endo-1.202** (100 MHz, CDCl₃) δ 140.4 (C8), 139.1 (C11), 137.5 (C1), 135.1 (C5), 129.7 (C9), 129.4 (C10), 87.7 (C1), 78.2 (C5), 67.3 (C3), 32.5 (C4), 18.8 (C7).

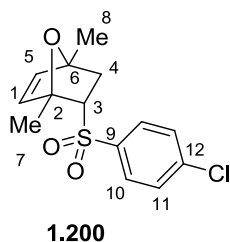


(1R,2S,4S)-2-(4-Chlorophenylsulfinyl)-1,4-dimethyl-7-oxabicyclo[2.2.1]hept-5-ene (1.194) (nb-4-98). TBSOTf (25 μ L, 0.11 mmol) was added dropwise to a solution of *p*-chlorophenyl-vinylsulfoxide (**-1.191**) (40 mg, 0.21 mmol) and 2,6-di-tert-butylpyridine (4.3 mg, 5 μ L, 0.02 mmol) in CH₃CN (100 μ L) at -30 °C. The mixture was stirred for 15 min, whereupon 2,5-dimethylfuran (41.5 mg, 46 μ L, 0.43 mmol) was added dropwise. The reaction was stored for 24 h at -30 °C (freezer). Saturated aqueous NaHCO₃ (800 μ L) was then added, with rapid stirring and the mixture was allowed to warm to room temperature. CH₂Cl₂ (2 mL) was added, and the layers were separated. The aqueous layer was then extracted with CH₂Cl₂ (3 x 4 mL), and the combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (30% to 66%) to give 57 mg (94%) of **1.194** as a mixture of *endo:exo* isomers (>25:1) as a clear oil; **endo-1.194** was separated via HPLC using a Chiral AD column (1 mL/min, 0% to 30% iPrOH/hexanes over 30 min) with the two enantiomers eluting at 18.35 min and 19.27 min in 98% de; ¹H NMR for **endo-1.194** (500 MHz, CDCl₃) δ 7.49-7.40 (comp, 4 H), 6.31 (d, *J* = 5.6 Hz, 1 H), 6.16 (d, *J* = 5.6 Hz, 1 H), 2.96 (dd, *J* = 8.6, 4.1 Hz, 1 H), 1.93 (dd, *J* = 12.0, 4.1 Hz, 1 H), 1.64 (dd, *J* = 11.9, 8.7 Hz, 1 H), 1.56 (s, 3 H), 1.51 (s, 3 H); ¹³C NMR for **endo-1.194** (125 MHz, CDCl₃) δ 142.7, 140.6, 136.9, 134.5, 129.4, 129.2, 86.3, 86.3, 71.5, 32.6, 18.6, 18.0; IR (neat) 3078, 1090 cm⁻¹; HRMS (CI) *m/z* calculated

for $C_{14}H_{16}O_2SCl^+$ (M+1) 283.0560; found, 283.0558; mass spectrum, 269, 283 (base), 285; $[\alpha]_D^{21}$ -178.9° (*c* 1.5, CH_2Cl_2).

NMR ASSIGNMENTS FOR *endo*-1.194:

1H NMR for *endo*-1.194 (500 MHz, $CDCl_3$) δ 7.49-7.40 (comp, 4 H, C10-H, C11-H), 6.31 (d, J = 5.6 Hz, 1 H, C1-H), 6.16 (d, J = 5.6 Hz, 1 H, C5-H), 2.96 (dd, J = 8.6, 4.1 Hz, 1 H, C3-H), 1.93 (dd, J = 12.0, 4.1 Hz, 1 H, C4-H), 1.64 (dd, J = 11.9, 8.7 Hz, 1 H, C4-H), 1.56 (s, 3 H, C7-H), 1.51 (s, 3 H, C8-H); ^{13}C NMR for *endo*-1.194 (125 MHz, $CDCl_3$) δ 142.7 (C9), 140.6 (C5), 136.9 (C12), 134.5 (C1), 129.4 (C10), 129.2 (C11), 86.3 (C7), 86.3 (C8), 71.5 (C3), 32.6 (C4), 18.6 (C8), 18.0 (C7).



(1R,2S,4S)-2-(4-Chlorophenylsulfonyl)-1,4-dimethyl-7-oxabicyclo[2.2.1]hept-5-ene (1.200) (nb-3-77). TBSOTf (25 μ L, 0.11 mmol) was added dropwise to a solution of *p*-chlorophenyl-vinylsulfoxide (-)-1.191 (40 mg, 0.21 mmol) and 2,6-di-tert-butylpyridine (4.3 mg, 5 μ L, 0.021 mmol) in CH_3CN (100 μ L) at -30 °C. The mixture was stirred for 15 min, whereupon 2,5-dimethylfuran (41.4 mg, 46 μ L, 0.43 mmol) was added dropwise. The reaction was stored for 24 h at -30 °C (freezer), whereupon 20%

TEA in MeOH (300 μ L) was added followed by Oxone (300 mg, 0.98 mmol). The suspension was stirred for 6 h, and H₂O (3 mL) was added. The mixture was extracted with Et₂O (4 x 3 mL) and the combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (15% to 50%) to give 56 mg (88%) of **1.200** as a mixture of *endo:exo* isomers (>25:1) as a white solid; **endo-1.200** was separated via HPLC using a Chiral OB column (1 mL/min, 0% to 20% iPrOH/hexanes over 30 min) with the two enantiomers eluting at 20.99 min and 25.11 min in 98% ee. The major *endo* isomer was recrystallized by slow evaporation from Et₂O to give X-ray quality crystals (mp: 108-110 °C); ¹H NMR for **endo-1.200** (500 MHz, CDCl₃) δ 7.80-7.75 (comp, 2 H), 7.55-7.50 (comp, 2 H), 6.35-6.32 (m, 2 H), 3.51 (dd, *J* = 8.9, 4.5 Hz, 1 H), 1.97 (dd, *J* = 11.7, 8.9 Hz, 1 H), 1.86 (dd, *J* = 11.7, 4.5 Hz, 1 H), 1.72 (s, 3 H), 1.57 (s, 3 H); ¹³C NMR for **endo-1.200** (125 MHz, CDCl₃) δ 140.3, 140.3, 139.1, 135.7, 129.6, 129.4, 87.6, 86.2, 69.9, 38.5, 19.0, 18.6; IR (neat) 2976, 1316 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₄H₁₆O₃SCl⁺ (*M*+1) 299.0509; found, 299.0511; mass spectrum, 123, 203 (base), 299; $[\alpha]_D^{28}$ +33.5° (*c* 0.2, CH₂Cl₂).

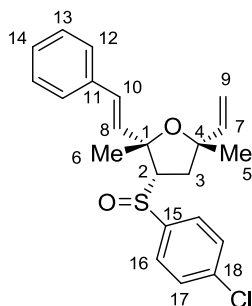
NMR ASSIGNMENTS FOR **endo-1.200**:

¹H NMR for **endo-1.200** (500 MHz, CDCl₃) δ 7.80-7.75 (comp, 2 H, C10-H), 7.55-7.50 (comp, 2 H, C11-H), 6.35-6.32 (m, 2 H, C1-H and C5-H), 3.51 (dd, *J* = 8.9, 4.5 Hz, 1 H, C3-H), 1.97 (dd, *J* = 11.7, 8.9 Hz, 1 H, C4-H), 1.86 (dd, *J* = 11.7, 4.5 Hz, 1 H, C4-H), 1.72 (s, 3 H, C7-H), 1.57 (s, 3 H, C8-H); ¹³C NMR for **endo-1.200** (125 MHz,

CDCl₃) δ 140.3 (C9), 140.3 (C11), 139.1 (C12), 135.7 (C10), 129.6 (C1), 129.4 (C5), 87.6 (C2), 86.2 (C6), 69.9 (C3), 38.5 (C4), 19.0 (C7), 18.6 (C8).

NMR ASSIGNMENTS FOR **exo-1.200**:

¹H NMR for **exo-1.200** (400 MHz, CDCl₃) δ 7.87-7.78 (m, 2H, C10-H), 7.56-7.47 (m, 2H, C11-H), 6.24 (d, J = 5.44 Hz, 1H, C1-H), 6.17 (d, J = 5.45 Hz, 1H, C5-H), 3.21 (dd, J = 8.1, 4.9 Hz, 1H, C3-H), 1.93 (s, 3H, C7-H), 1.84 (dd, J = 11.9, 4.8 Hz, 1H, C4-H), 1.61 (m, 4H, C4-H and C8-H); ¹³C NMR for **exo-1.200** (100 MHz, CDCl₃) δ 141.7 (C9), 140.2 (C11), 139.4 (C12), 139.0 (C10), 129.6 (C1), 129.5 (C5), 88.0 (C2), 85.4 (C6), 67.5 (C3), 38.4 (C4), 18.4 (C7), 17.0 (C8).



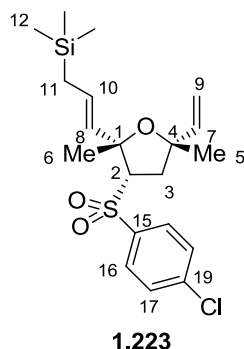
1.213

(2S,3S,5S)-3-((S)-4-Chlorophenylsulfinyl)-2,5-dimethyl-2-styryl-5-vinyltetrahydrofuran (1.213) (nb-2-291). Grubbs II catalyst (14 mg, 0.017 mmol) was added to a solution of oxanorbornene **1.194** (31 mg, 0.166 mmol) was in dichloroethane (500 μ L) immediately followed by styrene (344.3 mg, 380 μ L, 3.320 mmol). The reaction was stirred for 12 h at room temperature after which time the starting material had been consumed by TLC. The reaction was quenched with DMSO (50 μ L) and stirred

for 1 h before being concentrated under reduced pressure. The crude black semi-solid was purified *via* column chromatography (30% EtOAc/Hex) to yield **1.213** (40.5 mg, 63% yield) as a tan oil. ^1H NMR for **1.213** (500 MHz, CDCl_3) δ 7.58-7.54 (comp, 2 H), 7.52-7.48 (comp, 2 H), 7.43-7.36 (comp, 2 H), 7.36-7.31 (comp, 2 H), 7.27-7.23 (m, 1 H), 6.69-6.63 (d, $J = 15.9$ Hz, 1 H), 6.34 (d, $J = 15.9$, 1 H), 6.16-6.09 (dd, $J = 17.6$, 10.8 Hz, 1 H), 5.30-5.25 (dd, $J = 17.6$, 1.0 Hz, 1 H), 5.12-5.08 (dd, $J = 10.8$, 1.0 Hz, 1 H), 3.27-3.19 (dd, $J = 11.3$, 7.1 Hz, 1 H), 2.76 (dd, $J = 12.9$, 11.4 Hz, 1 H), 1.89-1.81 (dd, $J = 13.0$, 7.1 Hz, 1 H), 1.51 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR for **1.213** (125 MHz, CDCl_3) δ 143.8, 142.1, 137.5, 136.6, 131.0, 130.1, 129.6, 128.5, 127.8, 126.8, 126.0, 112.7, 83.3, 81.7, 74.8, 34.3, 28.2, 27.7; IR (neat) 2974.7, 1091.3; Mass Spectrum (CI) m/z 387.1185 [$\text{C}_{22}\text{H}_{24}\text{O}_2\text{SCl}$ (M+1) requires 287.1186], 380, 387 (base), 389.

NMR ASSIGNMENTS FOR **1.213**:

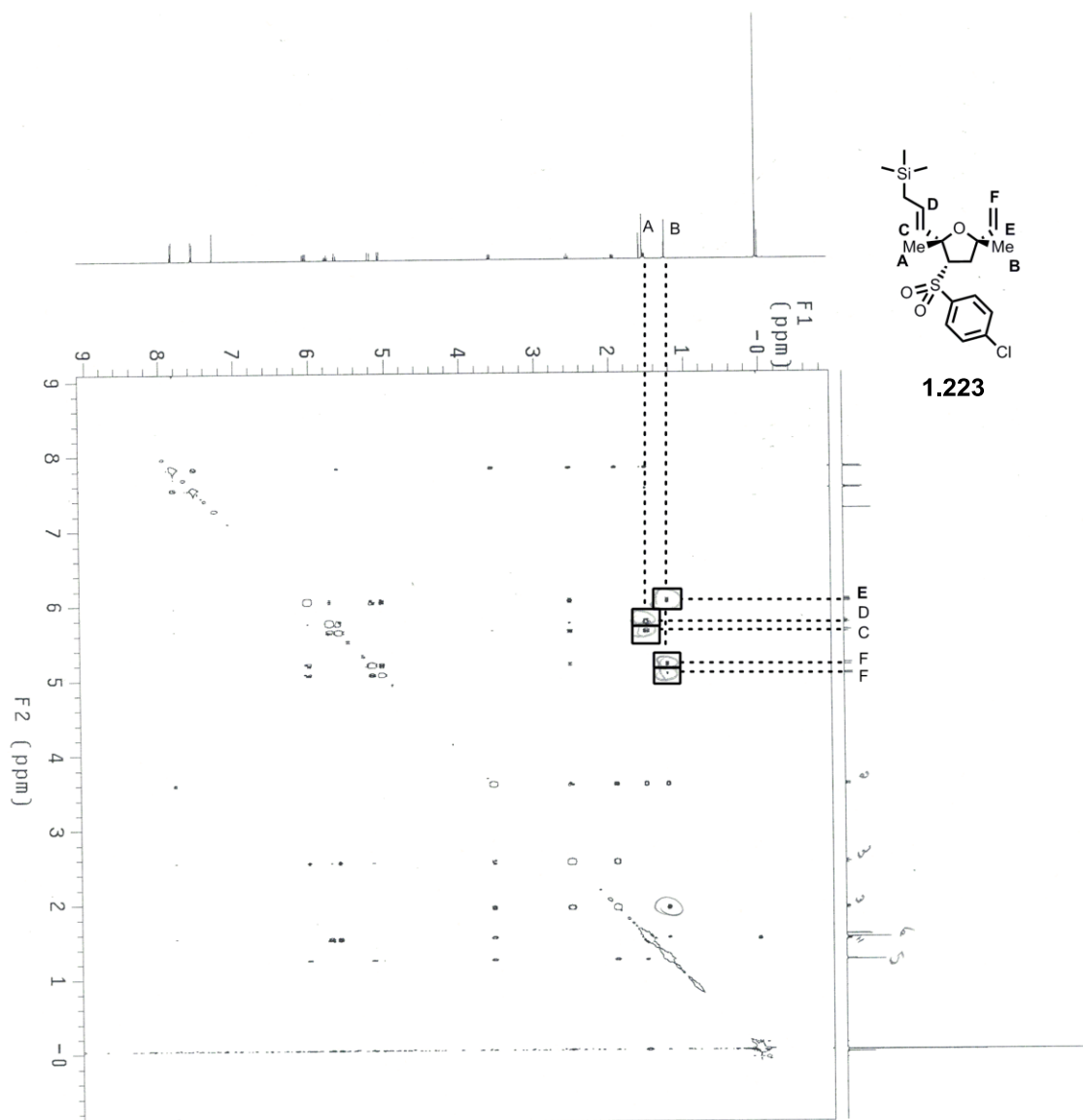
^1H NMR for **1.213** (500 MHz, CDCl_3) δ 7.58-7.54 (comp, 2 H, C17-H), 7.52-7.48 (comp, 2 H, C16-H), 7.43-7.36 (comp, 2 H, C12-H), 7.36-7.31 (comp, 2 H, C13-H), 7.27-7.23 (m, 1 H, C14-H), 6.69-6.63 (d, $J = 15.9$ Hz, 1 H, C10-H), 6.34 (d, $J = 15.9$ Hz, 1 H, C8-H), 6.16-6.09 (dd, $J = 17.4$, 10.8 Hz, 1 H, C7-H), 5.30-5.25 (dd, $J = 17.4$, 1.0 Hz, 1 H, C9-H), 5.12-5.08 (dd, $J = 10.8$, 1.0 Hz, 1 H, C9-H), 3.27-3.19 (dd, $J = 11.3$, 7.1 Hz, 1 H, C2-H), 2.76 (dd, $J = 12.9$, 11.4 Hz, 1 H, C3-H), 1.89-1.81 (dd, $J = 13.0$, 7.1 Hz, 1 H, C3-H), 1.51 (s, 3 H, C6-H), 1.33 (s, 3 H, C5-H); ^{13}C NMR for **1.213** (125 MHz, CDCl_3) δ 143.8 (C7), 142.1 (C15), 137.5 (C18), 136.6 (C11), 131.0 (C8), 130.1 (C10), 129.6 (C16), 128.5 (C13), 127.8 (C14), 126.8 (C12), 126.0 (C17), 112.7 (C9), 83.3 (C1), 81.7 (C4), 74.8 (C2), 34.3 (C3), 28.2 (C5), 27.7 (C6).

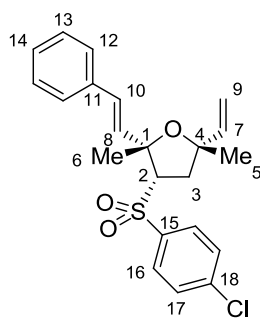


((E)-3-((2S,3S,5S)-3-(4-Chlorophenylsulfonyl)-2,5-dimethyl-5-vinyltetrahydrofuran-2-yl)allyl)trimethylsilane (1.223) (nb-3-116). Hoveyda-Grubbs II catalyst (53 mg, 0.08 mmol) was added to a solution of oxanorbornene **1.200** (1.0 g, 3.35 mmol) in 1,2-dichloroethane (10 mL) immediately followed by allyltrimethylsilane (5.74 mg, 7.99 mL, 50.25 mmol). After 4 h DMSO (300 μ L) was added and stirring continued for 12 h. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography with hexane/EtOAc (15%) to give 1.301 g (94%) of **1.223** as a clear oil: mp: 84-86 $^{\circ}$ C (clear rectangles from hexanes/EtOAc); ^1H NMR for **1.223** (500 MHz, CDCl_3) δ 7.85-7.79 (comp, 2 H), 7.57-7.51 (comp, 2 H), 6.03 (dd, J = 17.4, 10.8 Hz, 1 H), 5.75 (td, J = 15.3, 8.1, 8.1 Hz, 1 H), 5.62 (td, J = 15.2, 1.0, 1.0 Hz, 1 H), 5.18 (dd, J = 17.4, 1.0 Hz, 1 H), 5.05 (dd, J = 10.8, 0.9 Hz, 1 H), 3.58 (dd, J = 12.9, 6.3 Hz, 1 H), 2.54 (t, J = 12.5 Hz, 1 H), 1.93 (dd, J = 12.1, 6.3 Hz, 1 H), 1.53 (s, 3 H), 1.51 (m, 2 H), 1.23 (s, 3 H), 0.02 (s, 9 H); ^{13}C NMR for **1.223** (125 MHz, CDCl_3) δ 143.5, 140.6, 138.6, 130.0, 130.5, 128.4, 128.1, 112.8, 83.9, 80.3, 72.1, 39.1, 29.2, 27.8, 22.9, -1.8; IR (neat) 2954.1, 1090.37 cm^{-1} ; HRMS (CI) m/z calculated for $\text{C}_{20}\text{H}_{29}\text{O}_3\text{SSiCl}$ (M+1) 413.1373; found, 413.1367; mass spectrum, 397 (base), 399.

NMR ASSIGNMENTS FOR **1.223**:

^1H NMR for **1.223** (500 MHz, CDCl_3) δ 7.85-7.79 (comp, 2 H, C16-H), 7.57-7.51 (comp, 2 H, C17-H), 6.03 (dd, $J = 17.4, 10.8$ Hz, 1 H, C7-H), 5.75 (td, $J = 15.3, 8.1, 8.1$ Hz, 1 H, C10-H), 5.62 (td, $J = 15.2, 1.0, 1.0$ Hz, 1 H, C8-H), 5.18 (dd, $J = 17.4, 1.0$ Hz, 1 H, C9-H), 5.05 (dd, $J = 10.8, 0.9$ Hz, 1 H, C9-H), 3.58 (dd, $J = 12.9, 6.3$ Hz, 1 H, C2-H), 2.54 (t, $J = 12.5$ Hz, 1 H, C3-H), 1.93 (dd, $J = 12.1, 6.3$ Hz, 1 H, C3-H), 1.53 (s, 3 H, C6-H), 1.51 (m, 2 H, C11-H), 1.23 (s, 3 H, C5-H), 0.02 (s, 9 H, C12-H); ^{13}C NMR for **1.223** (125 MHz, CDCl_3) δ 143.5 (C7), 140.6 (C19), 138.6 (C15), 130.0 (C16), 130.5 (C17), 128.4 (C8), 128.1 (C10), 112.8 (C9), 83.9 (C4), 80.3 (C1), 72.1 (C2), 39.1 (3), 29.2 (C6), 27.8 (C5), 22.9 (C1), -1.8 (C12).



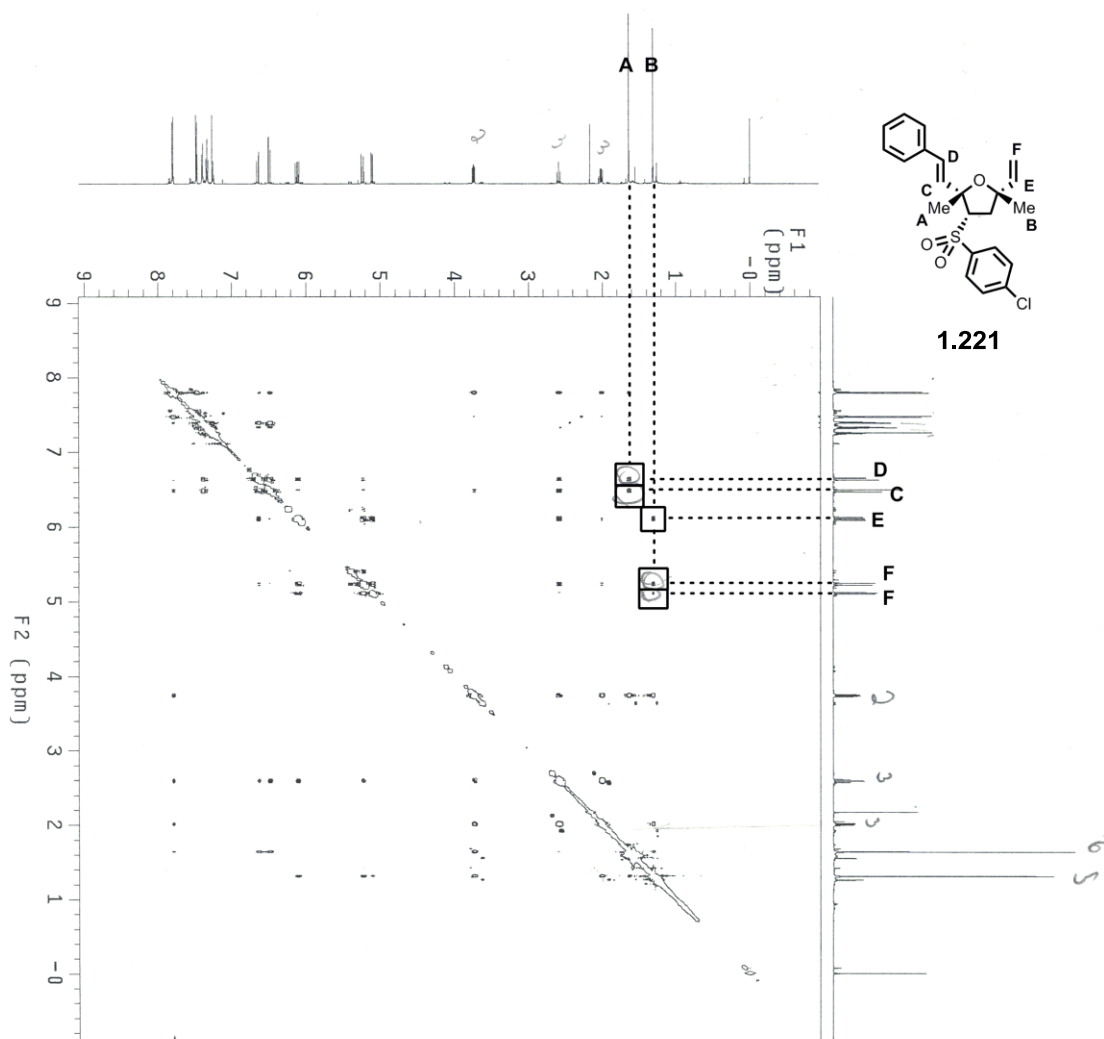


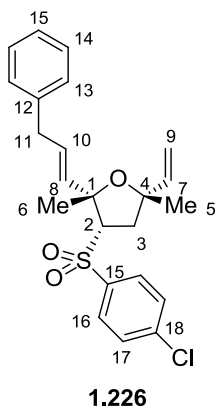
1.221

(2S,3S,5S)-3-(4-Chlorophenylsulfonyl)-2,5-dimethyl-2-styryl-5-vinyltetrahydrofuran (1.221) (nb-3-109). Grubbs II catalyst (21 mg, 0.025 mmol) was added to a solution of oxanorbornene **1.200** (150 mg, 0.502 mmol) in dichloroethane (4 mL) immediately followed by styrene (52.1 mg, 575 μ L, 5.02 mmol). The reaction was stirred for 4 h at room temperature after which time the starting material had been consumed by TLC. The reaction was quenched with DMSO (50 μ L) and stirred for 1 h before being concentrated under reduced pressure. The crude black semi-solid was purified *via* column chromatography (15% EtOAc/Hex) to yield **1.221** (188 mg, 93% yield) as a gray oil. ^1H NMR for **1.221** (500 MHz, CDCl_3) δ 7.82-7.77 (comp, 2 H), 7.50-7.45 (comp, 2 H), 7.39 (comp, 2 H), 7.34 (comp, 2 H), 7.26-7.22 (m, 1 H), 6.64 (d, J = 15.8 Hz, 1 H), 6.49 (d, J = 15.8 Hz, 1 H), 6.11 (dd, J = 17.4, 10.8 Hz, 1 H), 5.26-5.21 (dd, J = 17.4, 0.7 Hz, 1 H), 5.14-5.08 (dd, J = 10.8, 0.8 Hz, 1 H), 3.74 (dd, J = 12.9, 6.4 Hz, 1 H), 2.59 (t, J = 12.6 Hz, 1 H), 2.04-1.98 (dd, J = 12.2, 6.4, 1 H), 1.63 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR for **1.221** (125 MHz, CDCl_3) δ 143.1, 140.7, 138.0, 137.9, 136.7, 130.1, 130.0, 130.0., 129.5, 128.5, 127.6, 126.8, 113.2, 83.8, 80.8, 72.5, 39.0, 28.9, 27.6; IR (neat) 2976, 1089 cm^{-1} ; HRMS (CI) m/z calculated for $\text{C}_{22}\text{H}_{24}\text{O}_3\text{SCl}$ ($M+1$) 403.1135; found, 403.1132; mass spectrum, 380, 387 (base), 403.

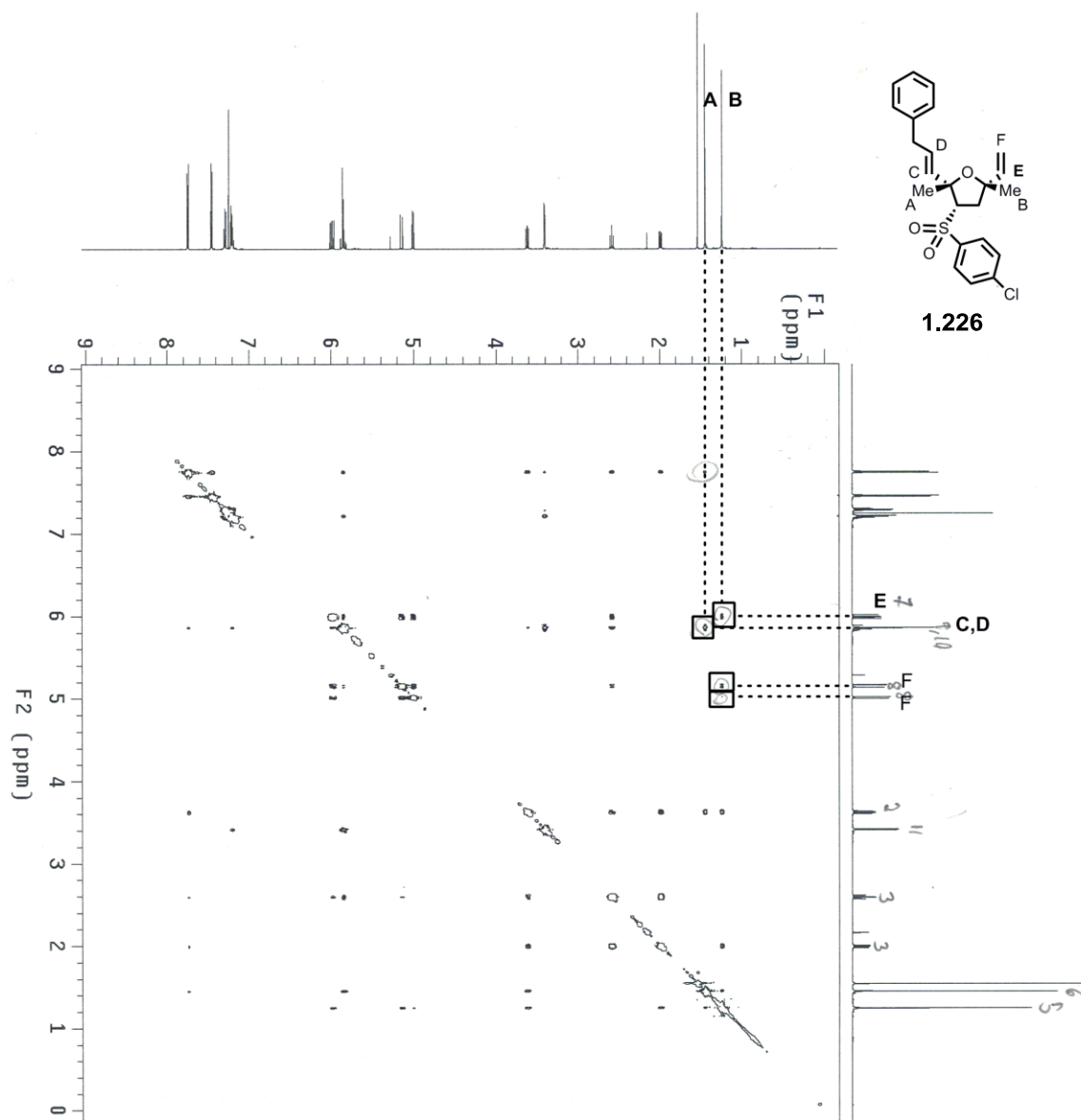
NMR ASSIGNMENTS FOR 1.221:

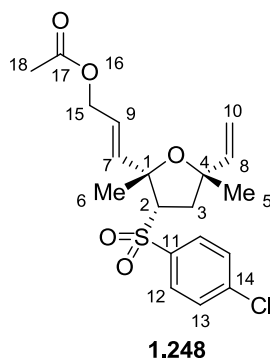
^1H NMR for **1.221** (500 MHz, CDCl_3) δ 7.82-7.77 (comp, 2H, C16-H), 7.50-7.45 (comp, 2 H, C17-H), 7.39 (comp, 2 H, C12-H), 7.34 (comp, 2 H, C13-H), 7.26-7.22 (m, 1 H, C14-H), 6.64 (d, $J = 15.8$ Hz, 1 H, C10-H), 6.49 (d, $J = 15.8$ Hz, 1 H, C8-H), 6.11 (dd, $J = 17.4, 10.8$ Hz, 1 H, C7-H), 5.26-5.21 (dd, $J = 17.4, 0.7$ Hz, 1 H, C9-H), 5.14-5.08 (dd, $J = 10.8, 0.8$ Hz, 1 H, C9-H), 3.74 (dd, $J = 12.9, 6.4$ Hz, 1 H, C2-H), 2.59 (t, $J = 12.6$ Hz, 1 H, C3-H), 2.04-1.98 (dd, $J = 12.2, 6.4$, 1 H, C3-H), 1.63 (s, 3 H, C6-H), 1.31 (s, 3 H, C5-H); ^{13}C NMR for **1.221** (125 MHz, CDCl_3) δ 143.1 (C7), 140.7 (C15), 138.0 (C18), 137.9 (C11), 130.1 (C10), 130.0 (C8), 130.0 (C16), 129.5 (C17), 128.5 (C13), 127.6 (C14), 126.8 (C12), 113.2 (C9), 83.8 (C6), 80.8 (C5), 72.5 (C2), 39.0 (C3), 28.9 (C6), 27.6 (C5).





(2S,3S,5S)-3-(4-Chlorophenylsulfonyl)-2,5-dimethyl-2-((E)-3-phenylprop-1-enyl)-5-vinyltetrahydrofuran (1.226) (nb-3-97). Grubbs II catalyst (2.5 mg, 0.003 mmol) was added to a solution of oxanorbornene **1.200** (20 mg, 0.067 mmol) in 1,2-dichloroethane (500 μ L) immediately followed by allylbenzene (79.4 mg, 89 μ L, 0.67 mmol). After 12 h DMSO (50 μ L) was added and stirring continued for 1 h. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography eluting with hexanes/EtOAc (15%) to give 25.9 mg (89%) of **1.226** as a clear oil. ^1H NMR for **1.226** (400 MHz, CDCl_3) δ 7.79-7.72 (comp., 2 H), 7.50-7.43 (comp., 2 H), 7.34-7.27 (comp., 2 H), 7.25-7.17 (comp., 3 H), 6.00 (dd, J = 17.4, 10.8 Hz, 1 H), 5.92-5.80 (comp., 2 H), 5.16 (dd, J = 17.4, 0.9 Hz, 1 H), 5.02 (dd, J = 10.8, 0.9 Hz, 1 H), 3.63 (dd, J = 12.9, 6.4 Hz, 1 H), 3.42 (d, J = 5.3 Hz, 2 H), 2.60 (t, J = 12.6 Hz, 1 H), 1.45 (d, J = 8.4 Hz, 1 H), 2.00 (s, 3 H), 1.26 (s, 3H); ^{13}C NMR for **1.226** (125 MHz, CDCl_3) δ 143.2, 140.7, 140.0, 138.2, 131.5, 130.0, 129.9, 129.5, 128.7, 128.3, 126.0, 113.0, 83.4, 80.5, 72.2, 38.8, 38.8, 28.6, 27.7; IR (neat) 2978, 1310, 1150 cm^{-1} ; HRMS (CI) m/z calculated for $\text{C}_{23}\text{H}_{29}\text{O}_3\text{SCl}$ (M+1) 434.15512; found, 434.15503; mass spectrum, 434 (base), 439, 442.

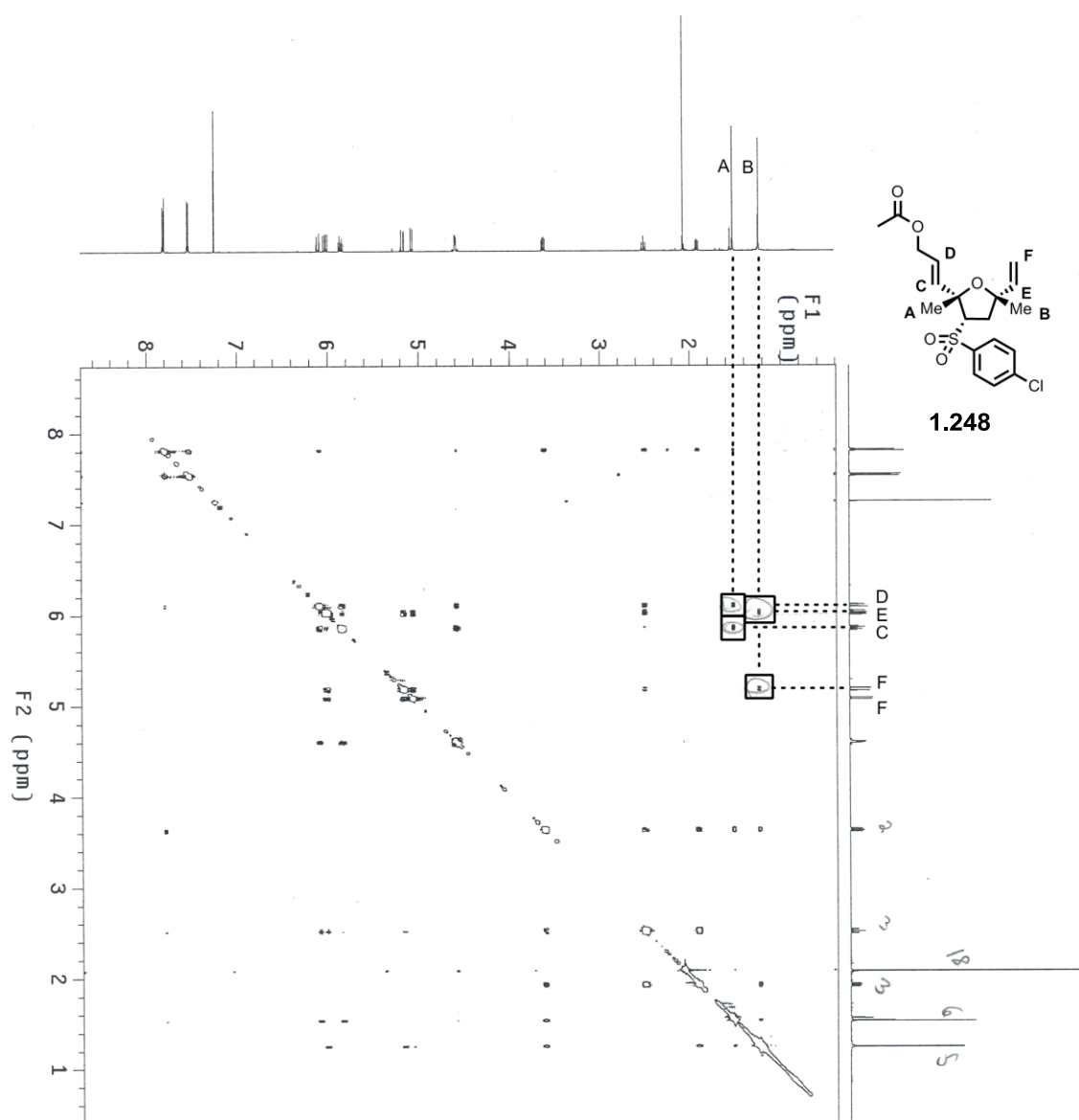


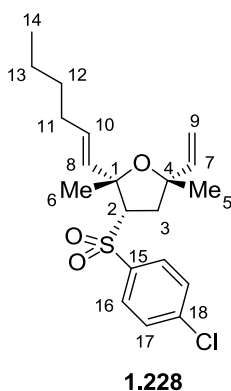


(E)-3-((2S,3S,5S)-3-(4-chlorophenylsulfonyl)-2,5-dimethyl-5-vinyltetrahydrofuran-2-yl)allyl acetate (1.248) (nb-3-270). Hoveyda-Grubbs II catalyst (6.3 mg, 0.01 mmol) in DCE (200 μ L) was added dropwise over 1 h to a solution of sulfone **1.200** (30 mg, 0.10 mmol), 1,4-cis-butene diacetate (103.7 mg, 96 μ L, 0.600 mmol), and DCE (100 μ L) under and atmosphere of ethylene. After 12 h DMSO (50 μ L) was added and stirring continued for 3 h. The solution was concentrated under reduced pressure to and the residue was purified by flash chromatography with pentane/Et₂O (30%) followed by a second flash chromatography with hexanes/EtOAc (25%) to give 21.7 mg (55%) **1.248** as a clear oil; ¹H NMR for **1.248** (500 MHz, CDCl₃) δ 7.86-7.79 (comp, 2 H), 7.58-7.52 (comp, 2 H), 6.11 (td, *J* = 15.4, 1.5, 1.5 Hz, 1 H), 6.04 (dd, *J* = 17.4, 10.8 Hz, 1 H), 5.91-5.82 (td, *J* = 15.4, 5.7, 5.7 Hz 1 H), 5.19 (dd, *J* = 17.4, 0.8 Hz, 1 H), 5.09 (dd, *J* = 10.8, 0.8 Hz, 1 H), 4.66-4.56 (m, 2 H), 3.68-3.58 (dd, *J* = 12.9, 6.4 Hz, 1 H), 2.52 (t, *J* = 12.57, 12.57 Hz, 1 H), 2.09 (s, 3 H), 1.94 (dd, *J* = 12.2, 6.4 Hz, 1 H), 1.54 (s, 3 H), 1.24 (s, 3 H); ¹³C NMR for **1.248** (125 MHz, CDCl₃) δ 170.7, 143.0, 140.8, 138.2, 134.1, 125.1, 113.2, 129.9, 129.6, 83.2, 80.8, 72.1, 64.1, 38.9, 28.9, 27.6, 20.9; IR (neat) 2979.0, 1738.0 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₉H₂₄O₅SCl (M+1) 399.1033; found, 399.1030; mass spectrum, 383 (base), 385.

NMR ASSIGNMENTS FOR 1.248:

^1H NMR for **1.248** (500 MHz, CDCl_3) δ 7.86-7.79 (comp, 2 H, C12-H), 7.58-7.52 (comp, 2 H, C13-H), 6.11 (td, $J = 15.4, 1.5, 1.5$ Hz, 1 H, C9-H), 6.04 (dd, $J = 17.4, 10.8$ Hz, 1 H, C8-H), 5.91-5.82 (td, $J = 15.4, 5.7, 5.7$ Hz, 1 H, C7-H), 5.19 (dd, $J = 17.4, 0.8$ Hz, 1 H, C10-H), 5.09 (dd, $J = 10.8, 0.8$ Hz, 1 H, C10-H), 4.66-4.56 (m, 2 H, C15-H), 3.68-3.58 (dd, $J = 12.9, 6.4$ Hz, 1 H, C2-H), 2.52 (t, $J = 12.57, 12.57$ Hz, 1 H, C3-H), 2.09 (s, 3 H, C18-H), 1.94 (dd, $J = 12.2, 6.4$ Hz, 1 H, C3-H), 1.54 (s, 3 H, C6-H), 1.24 (s, 3 H, C5-H); ^{13}C NMR for **1.248** (125 MHz, CDCl_3) δ 170.7 (C17), 143.0 (C8), 140.8 (C14), 138.2 (C11), 134.1 (C9), 129.9 (C12), 129.6 (C13), 125.1 (C7), 113.2 (C10), 83.2 (C1), 80.8 (C4), 72.1 (C2), 64.1 (C15), 38.9 (C3), 28.9 (C6), 27.6 (C5), 20.9 (C18).

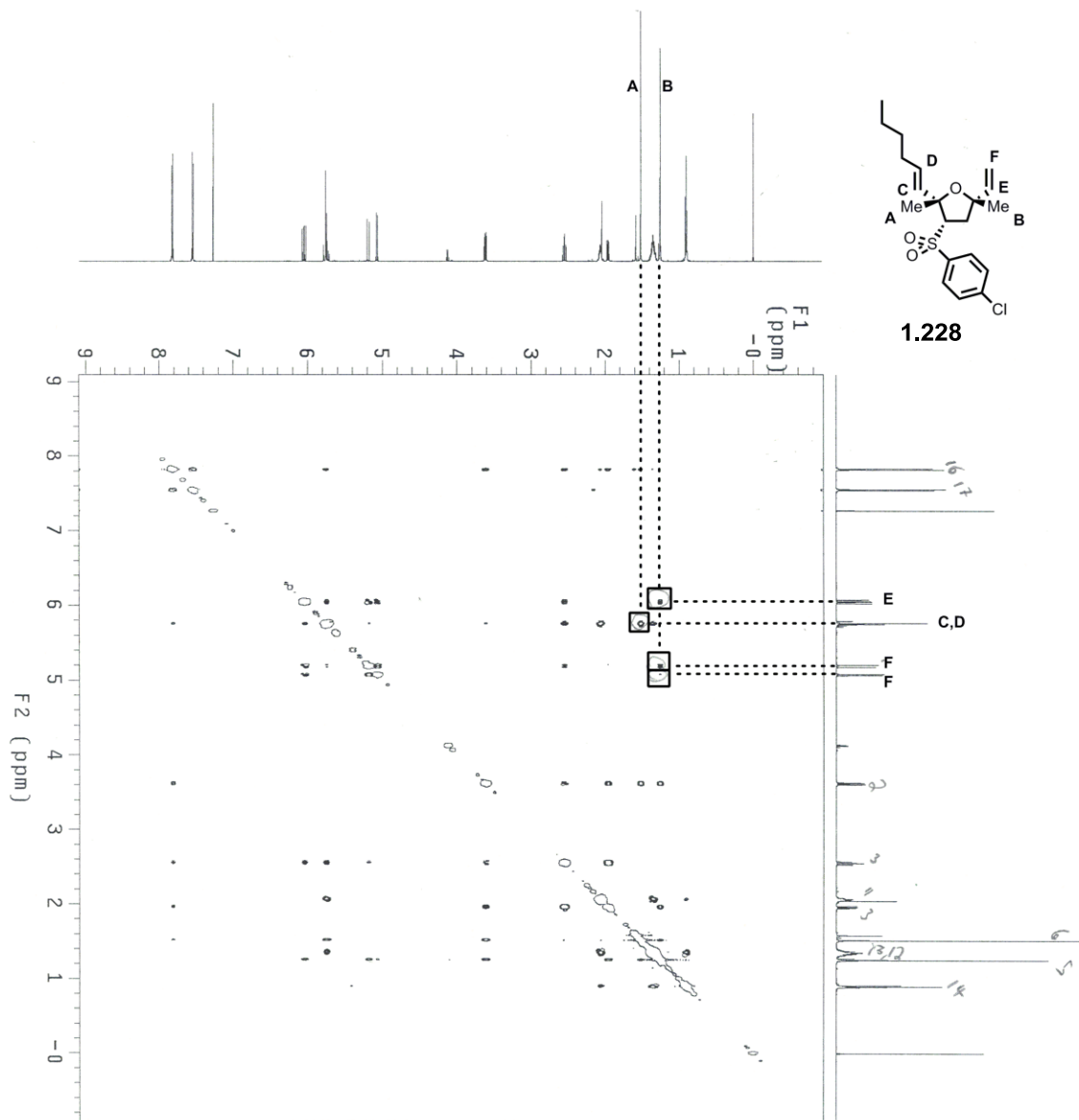


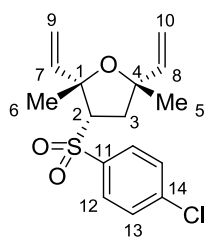


(2S,3S,5S)-3-(4-Chlorophenylsulfonyl)-2-((E)-hex-1-enyl)-2,5-dimethyl-5-vinyltetrahydrofuran (1.228) (nb-3-108). Hoveyda-Grubbs II catalyst (1.9 mg, 0.003 mmol) was added to a solution of oxanorbornene **1.200** (20 mg, 0.067 mmol) in 1,2-dichloroethane (500 μ L) immediately followed by 1-hexene (56.3 mg, 83 μ L, 0.67 mmol). After 12 h DMSO (50 μ L) was added and stirring continued for 1 h. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography with hexanes/EtOAc (15%) to give 20.1 mg (82%) of **1.228** as a clear oil; ^1H NMR for **1.228** (500 MHz, CDCl_3) δ 7.87-7.77 (comp, 2 H), 7.61-7.51 (comp, 2 H), 6.04 (dd, $J = 17.4, 10.8$ Hz, 1 H), 5.81-5.67 (comp, 2 H), 5.18 (dd, $J = 17.4, 0.9$ Hz, 1 H), 5.07 (dd, $J = 10.8, 0.9$ Hz, 1 H), 3.61 (dd, $J = 12.9, 6.4$ Hz, 1 H), 2.54 (t, $J = 12.5$ Hz, 1 H), 2.11-2.03 (m, 2 H), 1.95 (dd, $J = 12.1, 6.4$ Hz, 1 H), 1.51 (s, 3 H), 1.42-1.28 (m, 4 H), 1.25 (s, 3 H), 0.90 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR for **1.228** (125 MHz, CDCl_3) δ 143.4, 140.6, 139.4, 131.7, 130.0, 129.9, 129.5, 112.9, 83.6, 80.5, 72.2, 39.0, 32.0, 31.2, 28.9, 27.7, 22.3, 12.9; IR (neat) 2927.9, 1089.72 cm^{-1} ; HRMS (CI) m/z calculated for $\text{C}_{20}\text{H}_{29}\text{O}_3\text{SSiCl}$ ($M+1$) 383.1448; found, 383.1442; mass spectrum, 380 (base), 392.

NMR ASSIGNMENTS FOR 1.228:

^1H NMR for **1.228** (500 MHz, CDCl_3) δ 7.87-7.77 (comp, 2 H, C16-H), 7.61-7.51 (comp, 2 H, C17-H), 6.04 (dd, $J = 17.4, 10.8$ Hz, 1 H, C7-H), 5.81-5.67 (comp, 2 H, C8-H and C9-H), 5.18 (dd, $J = 17.4, 0.9$ Hz, 1 H, C9-H), 5.07 (dd, $J = 10.8, 0.9$ Hz, 1 H, C9-H), 3.61 (dd, $J = 12.9, 6.4$ Hz, 1 H, C2-H), 2.54 (t, $J = 12.5$ Hz, 1 H, C3-H), 2.11-2.03 (m, 2 H, C11-H), 1.95 (dd, $J = 12.1, 6.4$ Hz, 1 H, C3-H), 1.51 (s, 3 H, C6-H), 1.42-1.28 (m, 4 H, C13-H and C12-H), 1.25 (s, 3 H, C5-H), 0.90 (t, $J = 7.0$ Hz, 3 H, C14-H); ^{13}C NMR for **1.228** (125 MHz, CDCl_3) δ 143.4 (C7), 140.6 (C17), 139.4 (C16), 131.7 (C10), 130.0 (C16), 129.9 (C18), 129.5 (C17), 112.9 (C9), 83.6 (C1), 80.5 (C4), 72.2 (C2), 39.0 (C3), 32.0 (C11), 31.2 (C12), 28.9 (C6), 27.7 (C5), 22.3 (C13), 12.9 (C14).



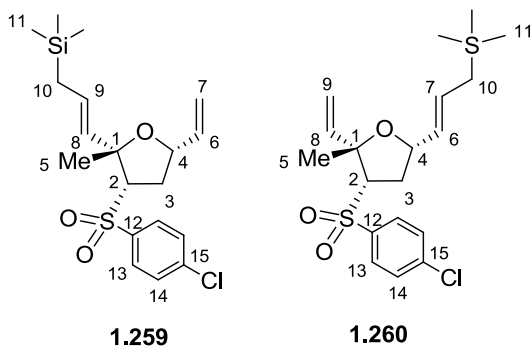


1.253

(2S,3S,5S)-3-(4-Chlorophenylsulfonyl)-2,5-dimethyl-2,5-divinyltetrahydrofuran (1.253) (nb-3-213). A solution of Hoveyda-Grubbs II catalyst (3 mg, 0.005 mmol) in DCE was sparged with ethylene gas for 5 min whereupon oxabicyclic **1.200** (29.6 mg, 0.099 mmol) was added and the solution was stirred under an ethylene atmosphere. After 6 h DMSO (50 μ L) was added and stirring continued for 3 h. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography with hexanes/EtOAc (15%) to give 25.2 mg (78%) of **1.253** as white crystals: mp: 117-120 $^{\circ}$ C (clear needles by Et₂O evaporation); ¹H NMR for **1.253** (500 MHz, CDCl₃) δ 7.90-7.76 (comp, 2 H), 7.69-7.45 (comp, 2 H), 6.23 (dd, J = 17.0, 10.7 Hz, 1 H), 6.05 (dd, J = 17.4, 10.8 Hz, 1 H), 5.39 (dd, J = 17.0, 1.5 Hz, 1H), 5.21 (comp, 2 H), 5.08 (dd, J = 10.8, 0.8 Hz, 1 H), 3.62 (dd, J = 13.0, 6.3 Hz, 1 H), 2.55 (t, J = 12.6, 12.6 Hz, 1 H), 1.91 (dd, J = 12.1, 6.3 Hz, 1 H), 1.56 (s, 3 H), 1.25 (s, H); ¹³C NMR for **1.253** (125 MHz, CDCl₃) δ 143.0, 140.7, 138.3, 138.2, 129.8, 129.7, 115.4, 113.2, 83.9, 80.7, 72.0, 38.9, 28.7, 27.6; IR (neat) 2979.0, 1146.0 cm^{-1} ; HRMS (CI) m/z calculated for C₁₆H₂₀O₃SCl (M+1) 327.0822; found, 327.0829; mass spectrum, 318, 327 (base), 329.

NMR ASSIGNMENTS FOR **1.253**:

^1H NMR for **1.253** (500 MHz, CDCl_3) δ 7.90-7.76 (comp, 2 H, C13-H), 7.69-7.45 (comp, 2 H, C12-H), 6.23 (dd, $J = 17.0, 10.7$ Hz, 1 H, C7-H), 6.05 (dd, $J = 17.4, 10.8$ Hz, 1 H, C8-H), 5.39 (dd, $J = 17.0, 1.5$ Hz, 1 H, C9-H), 5.21 (comp, 2 H, C9-H and C10-H), 5.08 (dd, $J = 10.8, 0.8$ Hz, 1 H, C10-H), 3.62 (dd, $J = 13.0, 6.3$ Hz, 1 H, C2-H), 2.55 (t, $J = 12.6, 12.6$ Hz, 1 H, C3-H), 1.91 (dd, $J = 12.1, 6.3$ Hz, 1 H, C3-H), 1.56 (s, 3 H, C6-H), 1.25 (s, 3 H, C5-H); ^{13}C NMR for **1.253** (125 MHz, CDCl_3) δ 143.0 (C8), 140.7 (C14), 138.3 (C11), 138.2 (C7), 129.8 (C13), 129.7 (C12), 115.4 (C9), 113.2 (C10), 83.9 (C1), 80.7 (C4), 72.0 (C2), (38.9 C3), 28.7 (C6), 27.6 (C5).



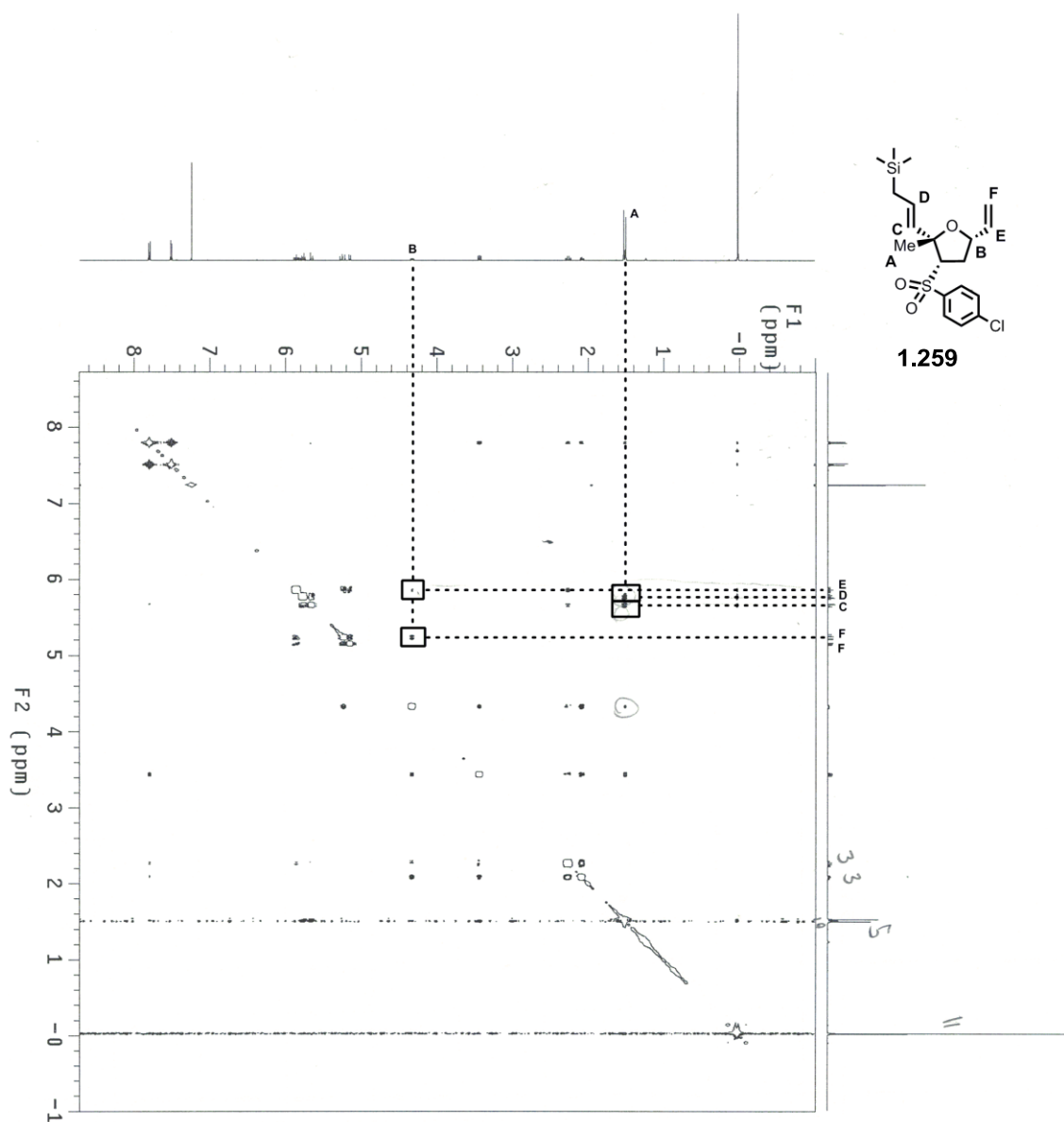
((E)-3-((2S,3S,5S)-3-(4-Chlorophenylsulfonyl)-2-methyl-5-vinyltetrahydrofuran-2-yl)allyl)trimethylsilane (1.259 and 1.260) (nb-4-206). Hoveyda-Grubbs 2nd generation catalyst (440 μg , 0.0007 mmol) in 1,2-dichloroethane (100 μL) was added to a solution of oxanorbornene **1.202** (20 mg, 0.07 mmol) and allyltrimethylsilane (79.8 mg, 111 μL , 0.70 mmol) in 1,2-dichloroethane (400 μL) at 70 $^\circ\text{C}$. The reaction was stirred at

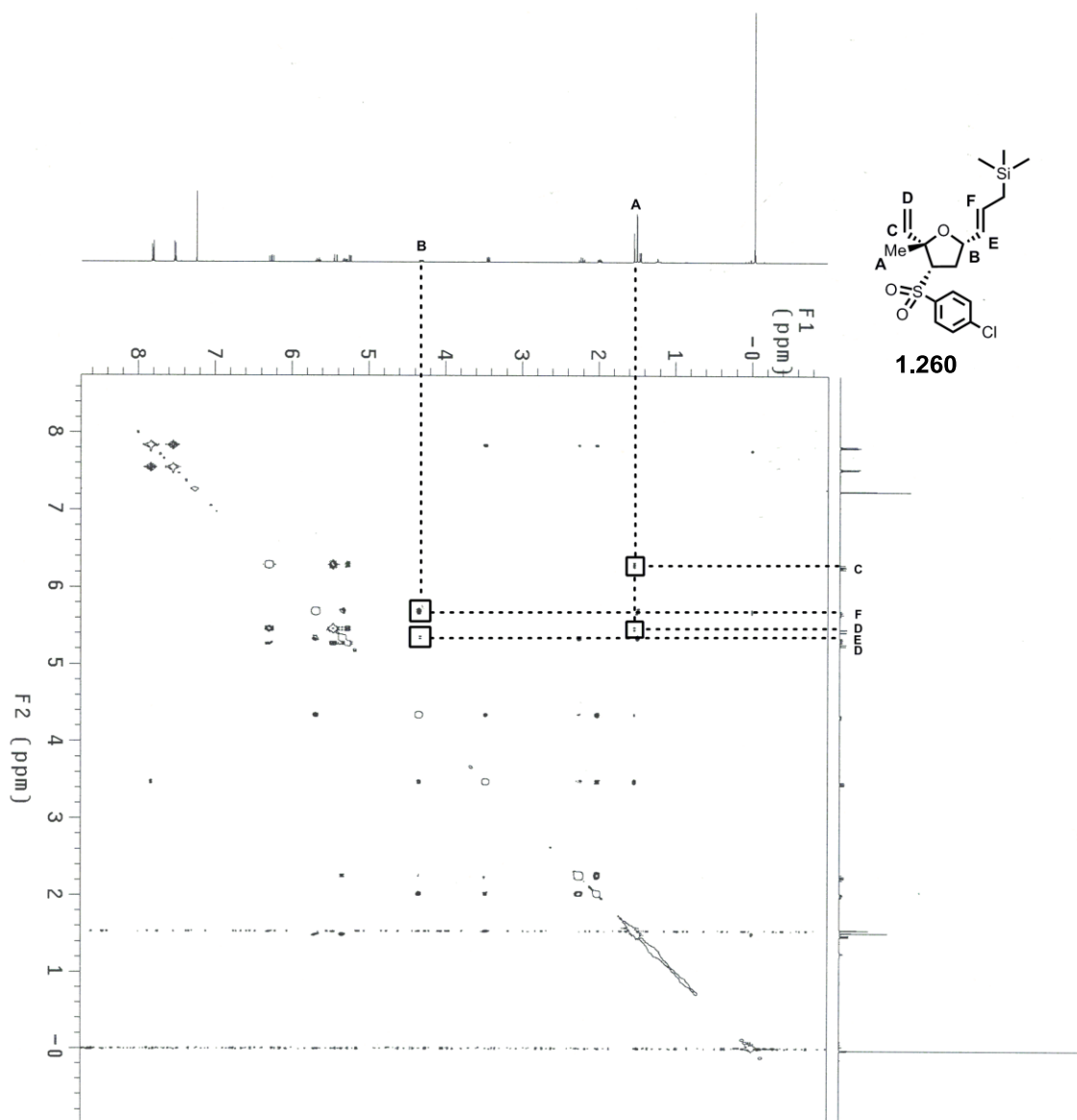
70 °C for 2 min, whereupon DMSO (40 μ L) was added and stirring continued for 12 h. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography with EtOAc/hexanes (10%) to give 19.5 mg (76%) of **1.259** and **1.260** as a mixture of regioisomers (12.3:1) as a clear oil; ^1H NMR for **1.259** (400 MHz, CDCl_3) δ 7.87-7.77 (comp, 2 H), 7.57-7.48 (comp, 2 H), 5.88 (ddd, $J = 17.1, 10.3, 7.0$ Hz, 1 H), 5.79 (dt, $J = 15.2, 8.2$ Hz, 1 H), 5.67 (dt, $J = 15.2, 1.0$ Hz, 1 H), 5.25 (dt, $J = 17.1, 1.2$ Hz, 1 H), 5.17 (dt, $J = 10.6, 0.9$ Hz, 1 H), 4.39-4.31 (m, 1 H), 3.46 (dd, $J = 12.2, 6.3$ Hz, 1 H), 2.28 (dt, $J = 12.2, 10.6$ Hz, 1 H), 2.10 (m, 1 H), 1.54-1.52 (m, 2 H), 1.52 (s, 3 H), 0.06-0.02 (m, 9 H); ^{13}C NMR for **1.259** (150 MHz, CDCl_3) δ 140.5, 138.6, 137.5, 129.9, 129.4, 128.6, 128.1, 117.4, 83.3, 77.6, 72.7, 35.0, 28.5, 22.8, -1.8; IR (neat) 2953, 1149, 1089 cm^{-1} ; HRMS (CI) m/z calculated for $\text{C}_{19}\text{H}_{28}\text{O}_3\text{SiSiCl}$ (M+1) 399.1217; found, 399.1213; mass spectrum, 383 (base), 385, 399.

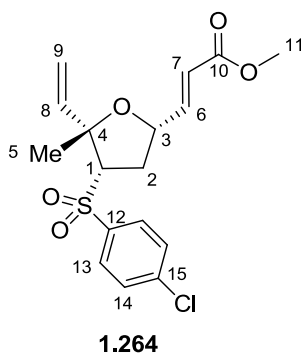
^1H NMR for **1.260** (400 MHz, CDCl_3) δ 7.86-7.79 (comp., 2 H), 7.58-7.51 (comp., 2 H), 6.29 (dd, $J = 16.9, 10.6$ Hz, 1 H), 5.74-5.63 (m, 1 H), 5.45 (dd, $J = 16.9, 1.7$ Hz, 1 H), 5.33 (tdd, $J = 15.1, 8.0, 1.2$ Hz, 1 H), 5.27 (dd, $J = 10.6, 1.7$ Hz, 1 H), 4.34 (ddd, $J = 10.4, 8.0, 5.0$ Hz, 1 H), 3.47 (dd, $J = 12.3, 6.2$ Hz, 1 H), 2.24 (dt, $J = 12.3, 10.6$ Hz, 1 H), 2.04-1.98 (m, 1 H), 1.52 (s, 3 H), 1.50-1.46 (dd, $J = 8.2, 1.2$ Hz, 1 H), -0.01 (s, 9 H); ^{13}C NMR for **1.260** (150 MHz, CDCl_3) δ 140.6, 138.8, 138.5, 132.2, 129.8, 129.6, 127.4, 115.4, 82.9, 78.2, 72.8, 35.2, 28.0, 22.9, -2.0; IR (neat) 2954, 1149, 1088 cm^{-1} ; HRMS (CI) m/z calculated for $\text{C}_{19}\text{H}_{28}\text{O}_3\text{SiSiCl}$ (M+1) 399.1217; found, 399.1219; mass spectrum, 381, 399, 431 (base).

NMR ASSIGNMENTS FOR 1.259:

^1H NMR for **1.259** (400 MHz, CDCl_3) δ 7.87-7.77 (comp, 2 H, C14-H), 7.57-7.48 (comp, 2 H, C13-H), 5.88 (ddd, $J = 17.1, 10.3, 7.0$ Hz, 1 H, C6-H), 5.79 (dt, $J = 15.2, 8.2$ Hz, 1 H, C9-H), 5.67 (dt, $J = 15.2, 1.0$ Hz, 1 H, C8-H), 5.25 (dt, $J = 17.1, 1.2$ Hz, 1 H, C7-H), 5.17 (dt, $J = 10.6, 0.9$ Hz, 1 H, C7-H), 4.39-4.31 (m, 1 H, C4-H), 3.46 (dd, $J = 12.2, 6.3$ Hz, 1 H, C2-H), 2.28 (dt, $J = 12.2, 10.6$ Hz, 1 H, C3-H), 2.10 (m, 1 H, C3-H), 1.54-1.52 (m, 2 H, C10-H), 1.52 (s, 3 H, C5-H), 0.06-0.02 (m, 9 H, C11-H); ^{13}C NMR for **1.259** (150 MHz, CDCl_3) δ 140.5, 138.6, 137.5, 129.9, 129.4, 128.6, 128.1, 117.4, 83.3, 77.6, 72.7, 35.0, 28.5, 22.8, -1.8.



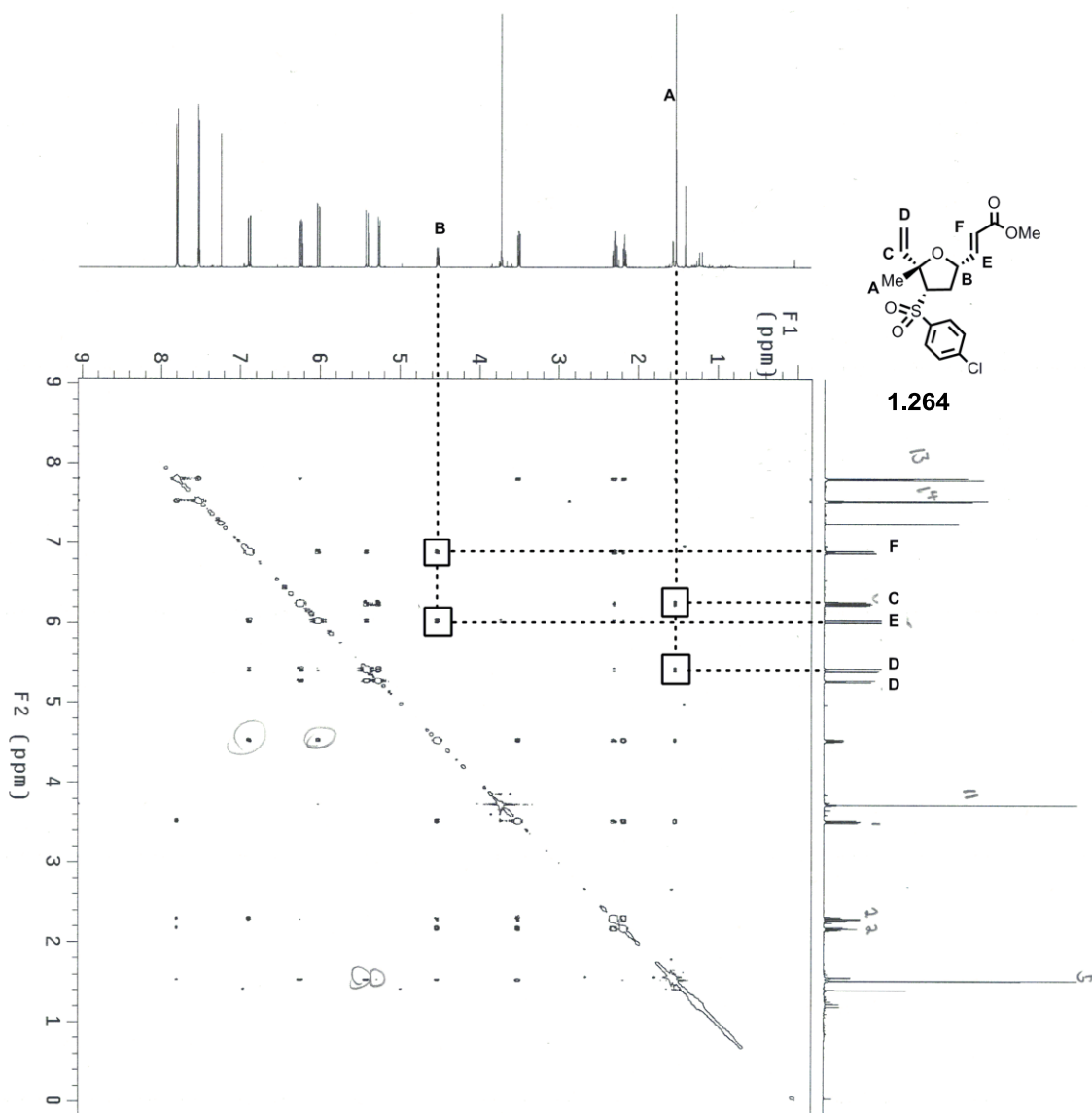


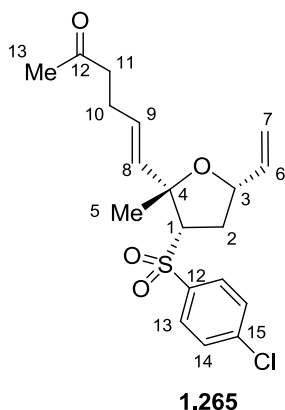


(E)-Methyl 3-((2S,3S,5S)-3-(4-chlorophenylsulfonyl)-2-methyl-5-vinyltetrahydrofuran-2-yl)acrylate (1.264) (nb-4-140). Hoveyda-Grubbs 2nd generation catalyst (440 μ g, 0.0007 mmol) was added to a solution of oxanorbornene **1.202** (20 mg, 0.07 mmol) in neat methylacrylate (301.1 mg, 315 μ L, 3.50 mmol) at 70 $^{\circ}$ C. The reaction was stirred at 70 $^{\circ}$ C for 2 min, whereupon DMSO (40 μ L) was added and the reaction was removed from the oil bath and stirring continued for 12 h. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography with Et₂O/pentane (50%) to give 17.3 mg (67%) of **1.264** as a single isomer as a clear oil; ¹H NMR for **1.264** (600 MHz, CDCl₃) δ 7.85-7.80 (comp, 2 H), 7.56-7.52 (comp, 2 H), 6.90 (dd, J = 15.6, 5.7 Hz, 1 H), 6.30-6.23 (dd, J = 17.0, 10.7, 1 H), 6.04 (dd, J = 15.7, 1.4 Hz, 1 H), 5.43 (dd, J = 17.0, 1.4 Hz, 1 H), 5.28 (dd, J = 10.7, 1.4, 1 H), 4.58-4.52 (m, 1 H), 3.74 (s, 3 H), 3.53 (dd, J = 8.6, 6.4, 1 H), 2.31 (dt, J = 12.1, 10.7 Hz, 1 H), 2.19 (m, 1 H), 1.54 (s, 1 H); ¹³C NMR for **1.264** (150 MHz, CDCl₃) δ 166.3, 145.4, 140.9, 138.1, 137.9, 129.9, 129.7, 122.0, 115.8, 83.9, 75.2, 72.5, 51.8, 34.6, 27.7; IR (neat) 2952, 1724, 1278 cm⁻¹; HRMS (CI) m/z calculated for C₁₇H₂₀O₅SCl (M+1) 371.0720; found, 371.0721; mass spectrum, 355, 368, 371 (base).

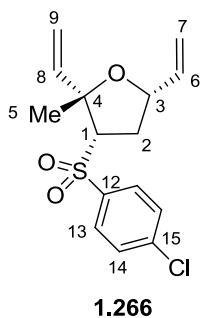
NMR ASSIGNMENTS FOR **1.264**:

^1H NMR for **1.264** (600 MHz, CDCl_3) δ 7.85-7.80 (comp, 2 H, C13-H), 7.56-7.52 (comp, 2 H, C14-H), 6.90 (dd, $J = 15.6, 5.7$ Hz, 1 H, C7-H), 6.30-6.23 (dd, $J = 17.0, 10.7$, 1 H, C8-H), 6.04 (dd, $J = 15.7, 1.4$ Hz, 1 H, C6-H), 5.43 (dd, $J = 17.0, 1.4$ Hz, 1 H, C9-H), 5.28 (dd, $J = 10.7, 1.4$, 1 H, C9-H), 4.58-4.52 (m, 1 H, C3-H), 3.74 (s, 3 H, C11-H), 3.53 (dd, $J = 8.6, 6.4$, 1 H, C1-H), 2.31 (dt, $J = 12.1, 10.7$ Hz, 1 H, C2-H), 2.19 (m, 1 H, C2-H), 1.54 (s, 1 H, C5-H); ^{13}C NMR for **1.264** (150 MHz, CDCl_3) δ 166.3 (C10), 145.4 (C7), 140.9 (C12), 138.1 (C15), 137.9 (C6), 129.9 (C13), 129.7 (C14), 122.0 (C8), 115.8 (C9), 83.9 (C4), 75.2 (C3), 72.5 (C1), 51.8 (C11), 34.6 (C2), 27.7 (C5).



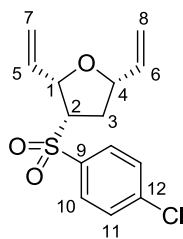


(E)-6-((2S,3S,5S)-3-(4-Chlorophenylsulfonyl)-2-methyl-5-vinyltetrahydrofuran-2-yl)hex-5-en-2-one (1.265) (nb-4-200). Hoveyda-Grubbs 2nd generation catalyst (440 μ g, 0.0007 mmol) in 1,2-dichloroethane (100 μ L) was added to a solution of oxanorbornene **1.202** (20 mg, 0.07 mmol) and 5-hexene-2-one (68.6 mg, 81 μ L, 0.70 mmol) in 1,2-dichloroethane (300 μ L) at reflux. The reaction was stirred at reflux for 15 min, whereupon DMSO (40 μ L) was added and the oil bath was removed; stirring continued for 12 h. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography with acetone/hexanes (10% to 20% gradient) to give 15.5 mg (59%) of **1.265** as a clear oil; ¹H NMR for **1.265** (600 MHz, CDCl₃) δ 7.87-7.74 (comp., 2 H), 7.60-7.49 (comp., 2 H), 5.86 (comp., 3 H), 5.26 (app. dt, J = 17.1, 1.1 Hz, 1 H), 5.21-5.17 (app. dt, J = 10.3, 0.9, 1 H), 4.41-4.28 (m, 1 H), 3.46 (dd, J = 12.1, 6.4 Hz, 1 H), 2.60-2.56 (m, 2 H), 2.41-2.34 (m, 2 H), 2.30-2.23 (m, 1 H), 2.17 (s, 1 H), 2.16 (s, 3 H), 2.11-2.03 (m, 1 H), 1.50 (s, 3 H); ¹³C NMR for **1.265** (150 MHz, CDCl₃) δ 208.2, 140.7, 138.5, 137.1, 131.3, 129.8, 129.7, 129.6, 117.9, 82.9, 77.8, 72.9, 42.8, 35.0, 29.9, 28.1, 26.2; IR (neat) 1713, 1325, 1148 cm⁻¹; HRMS (CI) m/z calculated for C₁₉H₂₄O₄SCl (M+1) 383.1084; found, 383.1077; mass spectrum, 369, 383 (base), 392.



(2S,3S,5S)-3-(4-Chlorophenylsulfonyl)-2-methyl-2,5-divinyltetrahydrofuran

(1.266) (nb-4-245). A solution of oxabicyclic **1.202** (20 mg, 0.07 mmol) in DCE (3 mL) was slowly sparged with ethylene gas while Hoveyda-Grubbs II catalyst (3 mg, 0.005 mmol) in DCE (100 μ L) was added. The slow sparge was continued for 3 h after which time all the starting material was consumed by TLC. DMSO (50 μ L) was added and stirring continued for 3 h. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography with hexanes/EtOAc (15%) to give 21.8 mg (99%) of **1.266** as white crystals: mp: 73-75 $^{\circ}$ C (clear needles by Et₂O evaporation); ¹H NMR for **1.266** (400 MHz, CDCl₃) δ 7.89-7.76 (comp, 2 H), 7.65-7.45 (comp, 2 H), 6.29 (dd, J = 17.0, 10.7 Hz, 1 H), 5.89 (ddd, J = 17.3, 10.2, 7.2 Hz, 1 H), 5.45 (dd, J = 17.0, 1.6 Hz, 1 H), 5.29-5.28 (m, 1 H), 5.27-5.23 (m, 1 H), 1H), 5.21-5.17 (m, 1 H), 4.45-4.32 (m, 1 H), 3.50 (dd, J = 12.3, 6.3 Hz, 1 H), 2.29 (dt, J = 12.2, 10.7 Hz, 1 H), 2.15-2.01 (m, 1 H), 1.53 (s, 3 H); ¹³C NMR for **1.266** (125 MHz, CDCl₃) δ 140.7, 138.4, 138.3, 137.1, 129.8, 129.6, 118.0, 115.5, 83.3, 77.9, 72.7, 34.9, 27.9; IR (neat) 2982, 1326, 1149 cm⁻¹; HRMS (CI) m/z calculated for C₁₅H₁₈O₃SCl (M+1) 313.0665; found, 313.0667; mass spectrum, 295 (base), 297, 313.



1.255

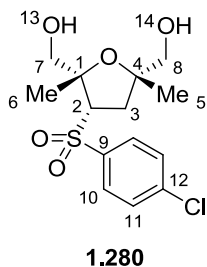
(2S,3S,5S)-3-(4-Chlorophenylsulfonyl)-2,5-divinyltetrahydrofuran

(1.255) (nb-3-256). A solution of Hoveyda-Grubbs II catalyst (18.5 mg, 0.030 mmol) in DCE was sparged with ethylene gas for 5 minutes whereupon oxabicyclic **1.203** (79.5mg, 0.295 mmol) was added and the solution was let stir under an atmosphere of ethylene. After 30 min DMSO (50 μ L) was added and stirring continued for 3 h. The solution was concentrated under reduced pressure and purified by flash chromatography with hexanes/EtOAc (25%) to give 61.9 mg of **1.255** (71%) as a yellow oil; ^1H NMR for **1.255** (400 MHz, CDCl_3) δ 7.84-7.72 (comp, 2 H), 7.60-7.43 (comp, 2 H), 6.29-6.14 (m, 1 H), 5.86 (m, 1 H), 5.38-5.21 (comp, 4 H), 5.20-5.11 (m, 1 H), 4.56 (m, 1 H), 4.35-4.18 (m, 1 H), 3.94-3.81 (m, 1 H), 2.28-2.08 (m, 1 H); ^{13}C NMR for **1.255** (100 MHz, CDCl_3) δ 140.6, 138.0, 136.6, 133.1, 129.9, 129.5, 119.1, 117.8, 79.9, 79.5, 66.8, 34.2; IR (neat) 3088.9, 1149.2; Mass Spectrum (CI) m/z 299.0507 (base) [$\text{C}_{14}\text{H}_{16}\text{O}_3\text{SCl}$ (M+1) requires 299.050] 297, 301.

NMR ASSIGNMENTS FOR 1.255:

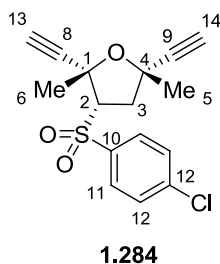
^1H NMR for **1.255** (400 MHz, CDCl_3) δ 7.84-7.72 (comp, 2 H, C10-H), 7.60-7.43 (comp, 2 H, C11-H), 6.29-6.14 (m, 1 H, C5-H), 5.86 (m, 1 H, C6-H), 5.38-5.16 (comp, 4 H, C7-H and C8-H), 4.56 (m, 1 H, C1-H), 4.35-4.18 (m, 1 H, C4-H), 3.94-3.81 (m, 1 H, C-H), 2.28-2.08 (m, 1 H, C3-H); ^{13}C NMR for **1.255** (100 MHz, CDCl_3) δ 140.6 (C12),

138.0 (C9), 136.6 (C6), 133.1 (C5), 129.9 (C10), 129.5 (C11), 119.1 (C7), 117.8 (C8), 79.9 (C1), 79.5 (C4), 66.8 (C2), 34.2 (C3).



((2S,3S,5S)-3-(4-Chlorophenylsulfonyl)-2,5-dimethyltetrahydrofuran-2,5-diyl)dimethanol (1.280) (nb-3-212). A stream of O₃/O₂ was bubbled through a solution of oxabicyclic **1.202** (30 mg, 0.10 mmol) and Sudan Red III (trace indicator) in acetone/H₂O (95:5, 3 mL) at 0 °C for five sec until the red color of the solution had disappeared. The reaction was flushed with N₂ for 30 sec whereupon it was warmed to room temperature. After 1 h the solution was concentrated under reduced pressure and the residue was azeotroped with benzene (2 x 5 mL). The residue was concentrated and dissolved in MeOH/CH₂Cl₂ (10:1, 3 mL) and cooled to 0 °C whereupon NaBH₄ (25 mg, 0.50 mmol) was added in a single portion. After 12 h saturated aqueous NH₄Cl (5 mL) and stirring continued for 15 min. The layers were separated and the aqueous portion was extracted with CH₂Cl₂ (3 x 5 mL). The combined organics were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography with hexanes/EtOAc (66% to 100%) to give 20.9 mg (62%) of **1.280** as a white foam; ¹H

NMR for **1.280** (600 MHz, CDCl₃) δ 7.90-7.86 (comp, 2 H), 7.62-7.57 (comp, 2 H), 4.29-4.15 (comp, 2 H), 3.76-3.67 (m, 2 H), 3.56 (m, 2 H), 3.37 (dd, J = 11.5, 10.0 Hz, 1 H), 3.05 (t, J = 12.7, 12.7 Hz, 1 H), 1.48 (dd, J = 12.1, 7.5 Hz, 1 H), 1.43 (s, 3 H), 1.10 (s, 3 H); ¹³C NMR for **1.280** (151 MHz, CDCl₃) δ 141.4, 137.4, 130.0, 129.7, 85.1, 83.2, 71.9, 67.9, 67.6, 35.8, 29.7, 27.6, 25.5; IR (neat) 3400.2, 1148.1 cm⁻¹; HRMS (CI) m/z calculated for C₁₄H₁₉O₅SCl (M+Na+1) 357.05339; found, 313.05382; mass spectrum, 357, 690 736 (base).

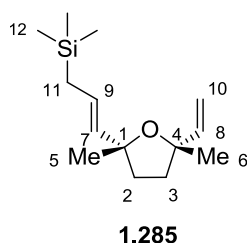


(2S,3S,5S)-3-(4-Chlorophenylsulfonyl)-2,5-diethynyl-2,5-dimethyltetrahydrofuran (1.284) (nb-3-241). A stream of O₃/O₂ was bubbled through a solution of oxabicyclo **1.202** (30 mg, 0.10 mmol) and Sudan Red III (trace indicator) in acetone/H₂O (95:5, 3 mL) at -78 °C for five sec. until the red color of the solution disappeared. The reaction was flushed with N₂ for 30 sec whereupon it was warmed to room temperature. After 1 h the solution was concentrated under reduced pressure and the residue was azeotroped with benzene (2 x 5 mL). residue was dissolved in MeOH (3 mL) to which was added K₂CO₃ (55 mg, 0.4 mmol) and dimethyl-1-diazo-2-oxopropylphosphonate (46 mg, 0.240 mmol). After 12 h H₂O (10 mL) was added the

layers were separated. The aqueous portion was extracted with Et₂O (2 x 10 mL) and the combined organics were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography with hexanes/EtOAc (15%) to give 16.7 mg (53%) of **1.284** as a clear oil (4:1 mixture of isomers); ¹H NMR for **1.284** (400 MHz, CDCl₃) δ 7.93-7.85 (comp, 2 H), 7.61-7.52 (comp, 2 H), 3.42-3.35 (dd, *J* = 12.4, 7.3 Hz, 1 H), 3.17 (t, *J* = 12.5 Hz, 1 H), 2.70 (s, 1 H), 2.54 (s, 1 H), 2.41-2.30 (dd, *J* = 12.6, 7.3 Hz, 1 H), 1.64-1.56 (s, 3H), 1.50 (s, 3 H); ¹³C NMR for **1.284** (151 MHz, CDCl₃) δ 141.2, 137.3, 130.5, 129.6, 85.9, 80.4, 77.7, 76.7, 73.4, 72.5, 71.1, 41.3, 30.4, 28.1; IR (neat) 3293.5, 1091.5 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₆H₁₆O₃SCl (M+1) 323.0509; found, 323.0511; mass spectrum, 323 (base), 325.

NMR ASSIGNMENTS FOR **1.284**:

¹H NMR for **1.284** (400 MHz, CDCl₃) δ 7.93-7.85 (comp, 2 H, C11-H), 7.61-7.52 (comp, 2 H, C12-H), 3.42-3.35 (dd, *J* = 12.4, 7.3 Hz, 1 H, C2-H), 3.17 (t, *J* = 12.5 Hz, 1 H, C3-H), 2.70 (s, 1 H, C13-H), 2.54 (s, 1 H, C14-H), 2.41-2.30 (dd, *J* = 12.6, 7.3 Hz, 1 H, C3-H), 1.64-1.56 (s, 3H, C6-H), 1.50 (s, 3 H, C5-H); ¹³C NMR for **1.284** (151 MHz, CDCl₃) δ 141.2 (C13), 137.3 (C10), 130.5 (C11), 129.6 (C12), 85.9 (C1), 80.4 (C4), 77.7 (C8), 76.7 (C9), 73.4 (C13), 72.5 (C14), 71.1 (C2), 41.3 (C3), 30.4 (C6), 28.1 (C5)

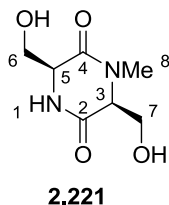


((E)-3-((2R,5S)-2,5-Dimethyl-5-vinyltetrahydrofuran-2-yl)allyl)trimethylsilane (1.285) (nb-3-186). Na-Hg amalgam (10% Na) (506 mg, 2.2 mmol) was added to a solution of sulfone **1.216** (89.5 mg, 0.22 mmol) in MeOH/H₂O (8:1) at 0 °C. After 6 h the reaction was filtered through celite with Et₂O. The combined organics were extracted with H₂O (2 x 10 mL) and dried (MgSO₄) and concentrated under reduced pressure (350 torr) at room temperature (product is volatile). The residue was purified by flash chromatography with pentane/Et₂O (10%) to give 41 mg (79%) of **1.285** as a volatile clear oil; ¹H NMR for **1.285** (400 MHz, CDCl₃) δ 5.93 (dd, *J* = 17.3, 10.7 Hz, 1 H), 5.65-5.52 (m, 1 H), 5.39 (td, *J* = 15.4, 1.2, 1.2 Hz, 1 H), 5.18 (dd, *J* = 17.3, 1.6 Hz, 1 H), 4.95 (dd, *J* = 10.7, 1.6 Hz, 1 H), 1.96-1.86 (m, 2 H), 1.86-1.76 (m, 2 H), 1.40 (dd, *J* = 8.1, 1.3 Hz, 2 H), 1.31 (s, 6 H), -0.03 (s, 9 H); ¹³C NMR for **1.285** (101 MHz, CDCl₃) δ 145.0, 135.2, 123.7, 111.3, 83.3, 83.1, 37.6, 37.2, 28.5, 27.7, 22.4, -2.0; IR (neat) 2964.3, 1247.8 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₄H₂₇OSi (M+1) 239.1831; found, 239.1830; mass spectrum, 167, 221 (base), 239.

NMR ASSIGNMENTS FOR 1.285:

¹H NMR for **1.285** (400 MHz, CDCl₃) δ 5.93 (dd, *J* = 17.3, 10.7 Hz, 1 H, C8-H), 5.65-5.52 (m, 1 H, C9-H), 5.39 (td, *J* = 15.4, 1.2, 1.2 Hz, 1 H, C7-H), 5.18 (dd, *J* = 17.3, 1.6 Hz, 1 H, C10-H), 4.95 (dd, *J* = 10.7, 1.6 Hz, 1 H, C10-H), 1.96-1.86 (m, 2 H, C2-H),

1.86-1.76 (m, 2 H, C3-H), 1.40 (dd, $J = 8.1, 1.3$ Hz, 2 H, C11-H), 1.31 (s, 6 H, C5-H and C6-H), -0.03 (s, 9 H, C12-H); ^{13}C NMR for **1.285** (101 MHz, CDCl_3) δ 145.0 (C8), 135.2 (C7), 123.7 (C9), 111.3 (C10), 83.3 (C4), 83.1 (C1), 37.6 (C2), 37.2 (C3), 28.5 (C5), 27.7 (C6), 22.4 (C11), -2.0 (C12).

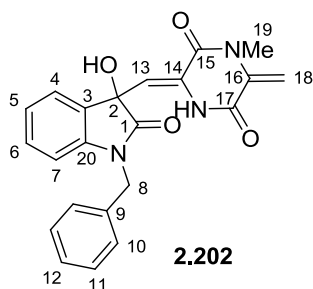


(3S,6S)-3,6-Bis(hydroxymethyl)-1-methylpiperazine-2,5-dione (2.221). (nb-7-32). Diisopropylethylamine (5.74 mL, 32.93 mmol) was added to a stirred suspension of Cbz-N-methyl-serine¹⁹⁵ **2.217** (2.78 g, 10.98 mmol), serine methylester **2.194** (1.88 g, 12.08 mmol), and Castro's reagent (5.86 g, 10.98 mmol) in anhydrous CH_2Cl_2 (30 mL) at -20°C . After 10 min at -20°C , the reaction mixture was warmed to room temperature and stirred for another 14 h, whereupon the solvent was removed under reduced pressure. The crude oil was dissolved in EtOAc (50 mL), and the solution was extracted with saturated aqueous NaHCO_3 (25 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were extracted with 1 M HCl (2 x 25 mL), brine (1 x 40 mL). The organic layer was dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with acetone/hexane (1:1) to acetone (100%) to provide 2.45 g of dipeptide **2.219** as colorless

oil. This was then dissolved in MeOH (200 mL) and put under argon atmosphere. Palladium on carbon (245 mg) was added in a single portion with rapid stirring, and the atmosphere was exchanged to hydrogen. The reaction was stirred for 2 h, after which time all the starting material was consumed by TLC. The solution was filtered and 37% NH₄OH was added (14 mL). The reaction was stirred for 15 h and concentrated under reduced pressure to a colorless oil. The residue was triturated with EtOAc (2 x 10 mL) and Et₂O (1 x 10 mL) and dried under hi-vac to give 1.28 g (62% based on **2.217**) of **2.221** as a mixture (1.0:0.2) of isomers as a white foam; ¹H NMR for **2.221** (major isomer) (400 MHz, DMSO) δ 8.15 (s, 1 H), 5.16 (d, *J* = 4.5 Hz, 1 H), 5.02 (d, *J* = 4.5 Hz, 1 H), 3.91-3.45 (comp, 6 H), 2.84 (comp, 3 H); ¹³C NMR for **2.221** (major isomer) (125 MHz, DMSO) δ 165.8, 164.6, 64.4, 63.6, 60.6, 57.5, 31.9; IR (neat) 3285, 1633, 1471, 1334 cm⁻¹; HRMS (CI) *m/z* calcd for C₇H₁₃N₂O₄⁺ (M+1), 189.0875; found 189.0876; mass spectrum, 190, 189 (base), 187.

NMR Assignments for 2.221 (major isomer):

¹H NMR for **2.221** (major isomer) (400 MHz, DMSO) δ 8.15 (s, 1 H, N-H), 5.16 (d, *J* = 4.5 Hz, 1 H, C6-OH), 5.02 (d, *J* = 4.5 Hz, 1 H, C7-OH), 3.91-3.45 (comp, 6 H, C3-H, C5-H, C6-H, C7-H), 2.84 (m, 3 H, C8-H); ¹³C NMR for **2.221** (major isomer) (125 MHz, DMSO) δ 165.8 (C2), 164.6 (C4), 64.4 (C3), 63.6 (C5), 60.6 (C6), 57.5 (C7), 31.9 (C8).

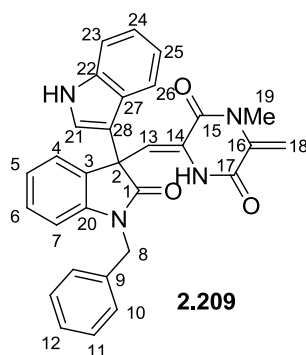


(Z)-3-((1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)methylene)-1-methyl-6-methylenepiperazine-2,5-dione (2.202) (nb-7-87). Freshly distilled mesyl chloride (310 mg, 0.21 mL, 2.66 mmol) was added dropwise over 1 min to a solution of diketopiperazine **2.221** (200 mg, 1.06 mmol), dry triethylamine (537.2 mg, 0.74 mL, 5.31 mmol) in dry DMF (10 mL) at 0 °C. The reaction was let stir for 1 h at 0 °C, after which time the mixture was a dark orange cloudy suspension. The reaction was allowed to warm to room temperature and was stirred for 1 h. The suspension was filtered through a cotton plug under nitrogen into a flask charged with N-benzyl-isatin **2.201** (754 mg, 3.18 mmol), anhydrous K₂CO₃ (1.17 g, 8.48 mmol), and MgSO₄ (510 mg, 4.24 mmol). The suspension was stirred in darkness for 36 h, after which time all starting material was consumed by TLC. The reaction mixture was filtered through a Buchner funnel into a flask containing 50% saturated aqueous NH₄Cl (20 mL) and stirred for 10 min before CH₂Cl₂ (20 mL) was added. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL), and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (30% to 70% gradient) to give 293 mg (71% based on **2.221**) of **2.202** as a gray foam: ¹H NMR for **2.202** (400 MHz, DMSO) δ 10.20 (s, 1 H), 7.61 (s, 1 H, C13), 7.40 (dd, *J* = 7.3, 1.0 Hz, 1 H), 7.38-7.19 (comp, 6 H), 7.07 (dt, *J* = 7.6, 7.6, 0.8 Hz, 1 H), 6.93 (d, *J* = 7.8

Hz, 1 H), 5.64 (d, $J = 1.3$ Hz, 1 H), 5.55 (s, 1 H), 5.17 (s, 1 H), 4.92 (d, $J = 15.7$ Hz, 1 H), 4.84 (d, $J = 15.7$ Hz, 1 H), 3.19 (s, 3 H); ^{13}C NMR for **2.202** (125 MHz, DMSO) δ 175.0, 155.2, 154.5, 141.5, 136.4, 135.8, 130.9, 130.5, 129.9, 128.6, 127.4, 127.2, 124.2, 123.2, 112.4, 109.8, 103.2, 76.6, 54.8, 30.1; IR (neat) 3299, 1633, 1693, 1610, 1384 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{NaO}_4^+$ (M+Na), 412.12678; found 412.12688; mass spectrum, 390, 412 (base), 413, 536.

NMR Assignments for **2.202**:

^1H NMR for **1.202** (400 MHz, DMSO) δ 10.20 (s, 1 H, N-H), 7.61 (s, 1 H, C13-H), 7.40 (dd, $J = 7.3, 1.0$ Hz, 1 H, C6-H), 7.38-7.19 (comp, 6 H, C4-H, C10-H, C11-H, C12-H), 7.07 (dt, $J = 7.6, 7.6, 0.8$ Hz, 1 H, C5-H), 6.93 (d, $J = 7.8$ Hz, 1 H, C7-H), 5.64 (d, $J = 1.3$ Hz, 1 H, C18-H), 5.55 (s, 1 H, C18-H), 5.17 (s, 1 H, C2-OH), 4.92 (d, $J = 15.7$ Hz, 1 H, C8-H), 4.84 (d, $J = 15.7$ Hz, 1 H, C8-H), 3.19 (s, 3 H, C19-H); ^{13}C NMR for **2.202** (125 MHz, DMSO) δ 175.0 (C1), 155.2 (C15), 154.5 (C17), 141.5 (C20), 136.4 (C16), 135.8 (C9), 130.9 (C4), 130.5 (C7), 129.9 (C3), 128.6 (C11), 127.4 (C14), 127.2 (C10), 124.2 (C5), 123.2 (C6), 112.4 (C12), 109.8 (C13), 103.2 (C18), 76.6 (C2), 54.8 (C8), 30.1 (C19).

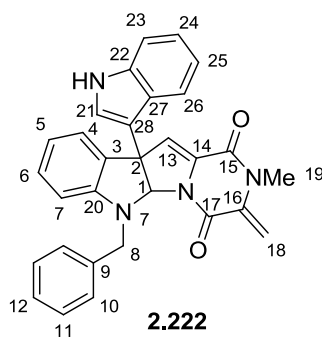


(Z)-3-((1-Benzyl-2-oxo-3,3'-biindolin-3-yl)methylene)-1-methyl-6-methylenepiperazine-2,5-dione (2.209) (nb-7-142). Freshly distilled TMSOTf (19 μ L, 0.105 mmol) was added to a suspension of tertiary alcohol **2.202** (20 mg, 0.051 mmol) and 2,6-di-*tert*-butylpyridine (20.4 mg, 24 μ L, 0.108 mmol) in dry dichloroethane. The suspension was stirred for 1 h, after which time it became a homogenous solution. The reaction was cooled to 0 $^{\circ}$ C and indole (30 mg, 0.255 mmol) followed by TMSOTf (11.1 mg, 9 μ L, 0.051 mmol) were added. After 30 min, the reaction was warmed to room temperature and stirred for 1.5 h until all the starting material was consumed by TLC, whereupon saturated aqueous NaHCO₃ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL), and the combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (40% to 50%) to give 17.7 mg (71%) of **2.209** as a white solid: mp 154-156 $^{\circ}$ C; ¹H NMR for **2.209** (400 MHz, DMSO) δ 11.18 (d, *J* = 2.1 Hz, 1 H), 10.30 (s, 1 H), 7.49 (d, *J* = 2.6 Hz, 1 H), 7.45-7.39 (comp, 2 H), 7.39-7.26 (comp, 5 H), 7.25-7.16 (comp, 2 H), 7.10-6.93 (comp, 2 H), 6.67-6.57 (m, 1 H), 6.50 (d, *J* = 8.0 Hz, 1 H), 6.09 (s, 1 H), 5.56 (d, *J* = 1.1 Hz, 1 H), 5.09 (comp, 3 H), 3.21 (s, 3 H); ¹³C NMR for **2.209** (125 MHz, DMSO) δ 177.3, 155.7, 154.9, 140.9, 137.1, 136.8, 135.7, 134.0, 130.5, 128.7, 128.6, 127.9, 127.8, 125.6, 124.2, 124.0,

123.6, 121.4, 118.9, 118.2, 112.9, 111.9, 110.0, 109.8, 102.7, 52.4, 30.2; IR (neat) 3328, 1685, 1609, 1386 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{30}\text{H}_{25}\text{N}_4\text{O}_3^+$ (M+1), 489.19212; found 489.19215; mass spectrum, 183, 489, 511 (base).

NMR Assignments for 2.209:

^1H NMR for **2.209** (400 MHz, DMSO) δ 11.18 (d, $J = 2.1$ Hz, 1 H, N-H), 10.30 (s, 1 H, indole-NH), 7.49 (d, $J = 2.6$ Hz, 1 H, C26-H), 7.45-7.39 (comp, 2 H, C23-H, C21-H), 7.39-7.26 (comp, 5 H, C10-H, C11-H, C12-H), 7.25-7.16 (comp, 2 H, C5-H, C6-H), 7.10-6.93 (comp, 2 H, C24-H, C25-H), 6.67-6.57 (m, 1 H, C4-H), 6.50 (d, $J = 8.0$ Hz, 1 H, C7-H), 6.09 (s, 1 H, C13-H), 5.56 (d, $J = 1.1$ Hz, 1 H, C18-H), 5.09 (comp, 3 H, C8-H, C18-H), 3.21 (s, 3 H, C19-H); ^{13}C NMR for **2.209** (125 MHz, DMSO) δ 177.3 (C1), 155.7 (C15), 154.9 (C17), 140.9 (C20), 137.1 (C16), 136.8 (C22), 135.7 (C9), 134.0 (C3), 130.5 (C6), 128.7 (C10), 128.6 (C14), 127.9 (C11), 127.8 (C27), 125.6 (C5), 124.2 (C4), 124.0 (C21), 123.6 (C24), 121.4 (C25), 118.9 (C26), 118.2 (C7), 112.9 (C13), 111.9 (C28), 110.0 (C23), 109.8 (C18), 102.7 (C2), 52.4 (C8), 30.2 (C19).

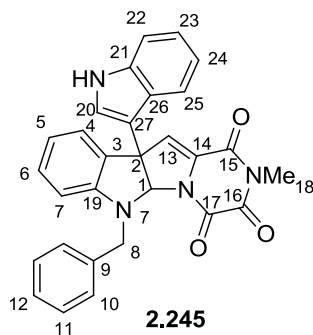


(Z)-3-(1-Benzyl-3,3'-biindolin-3-yl)-1-methyl-6-methylenepiperazine-2,5-dione

(2.222) (nb-7-224). $\text{AlH}_3\text{NEtMe}_2$ (0.5 M in toluene, 167.4 mg, 0.2 mL, 0.102 mmol) was added dropwise over 5 sec to a solution of oxindole **2.209** (25 mg, 0.051 mmol) in dry THF (5 mL) at 0 °C. The dark yellow solution was immediately quenched with AcOH (2 M, 3 mL). The solution was stirred for 20 sec, whereupon water (5 mL) was added along with EtOAc (4 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 4 mL) and the combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by preparative TLC eluting with 15% EtOAc/ CH_2Cl_2 to give 12.9 mg (54%) of **2.222** as a yellow solid: mp 169-171 °C; ^1H NMR for **2.222** (400 MHz, CD_3CN) δ 9.27 (s, 1 H), 7.44-7.35 (comp, 3 H), 7.30-7.20 (comp, 3 H), 7.15-7.02 (comp, 3 H), 6.99-6.93 (m, 1 H), 6.73 (ddd, J = 8.0, 7.0, 1.0 Hz, 1 H), 6.70-6.58 (comp, 3 H), 6.53 (s, 1 H), 6.30 (s, 1 H), 5.65 (d, J = 1.4 Hz, 1 H), 4.99 (dd, J = 8.7, 7.3 Hz, 2 H), 4.77 (d, J = 16.0 Hz, 1 H), 3.25-3.20 (s, 3 H); ^{13}C NMR for **2.222** (125 MHz, CD_3CN) δ 156.7, 155.7, 150.7, 139.6, 139.4, 138.2, 133.5, 131.5, 129.6, 129.4, 128.7, 128.2, 125.9, 125.4, 124.1, 123.3, 122.9, 120.3, 120.0, 199.5, 116.9, 112.7, 108.8, 102.6, 89.3, 59.7, 51.7, 30.1; IR (neat) 3344, 1684, 1603, 1420 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{30}\text{H}_{25}\text{N}_4\text{O}_2$ (M+1), 473.19720; found 473.19687; mass spectrum, 473, 495 (base), 497.

NMR Assignments for **2.222**:

^1H NMR for **2.222** (400 MHz, CD_3CN) δ 9.27 (s, 1 H, N-H), 7.44-7.35 (comp, 3 H, C12-H, C26-H, C23-H), 7.30-7.20 (comp, 3 H, C11-H, C21-H), 7.15-7.02 (comp, 3 H, C10-H, C2-H, C4-H), 6.99-6.93 (m, 1 H, C25-H), 6.73 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1 H, C5-H), 6.70-6.58 (comp, 3 H, C5-H, C6-H, C7-H), 6.53 (s, 1 H, C1-H), 6.30 (s, 1 H, C13-H), 5.65 (d, $J = 1.4$ Hz, 1 H, C18-H), 4.99 (dd, $J = 8.7, 7.3$ Hz, 2 H, C8-H, C18-H), 4.77 (d, $J = 16.0$ Hz, 1 H, C8-H), 3.25-3.20 (s, 3 H, C19-H); ^{13}C NMR for **2.222** (125 MHz, CD_3CN) δ 156.7 (C15), 155.7 (C17), 150.7 (C20), 139.6 (C9), 139.4 (C16), 138.2 (C22), 133.5 (C3), 131.5 (C14), 129.6 (C4), 129.4 (C11), 128.7 (C10), 128.2 (C12), 125.9 (C6), 125.4 (C27), 124.1 (C5), 123.3 (C24), 122.9 (C25), 120.3 (C26), 120.0 (C23), 119.5 (C7), 116.9 (C28), 112.7 (C21), 108.8 (C1), 102.6 (C18), 89.3 (C13), 59.7 (C2), 51.7 (C8), 30.1 (C19)



(Z)-3-(1-Benzyl-3,3'-biindolin-3-yl)-1-methyl-2,3,6-trioxo-6-methylenepiperazine-2,5-dione (2.245) (nb-7-241). Osmium tetroxide (2.5% in butanol) (18.6 mg, 23 μL , 0.0017 mmol) was added to a solution of diene **2.222** (32.5 mg, 0.069 mmol) and N-methylmorpholine N-oxide (12 mg, 0.104 mmol) in acetone/ H_2O (9:1) (2.5 mL) at 0 $^\circ\text{C}$. The reaction was stirred at

0 °C for 3 h, whereupon saturated aqueous sodium thiosulfate (4 mL) and EtOAc (5 mL) were added and the mixture was stirred at room temperature for 15 min before the layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with pH 7 phosphate buffer containing 0.1% EDTA (2 x 6 mL). The organic layer was concentrated under reduced pressure and the crude diol was dissolved in acetone/H₂O (3.5 mL). 2,6-Lutidine (16 µL, 0.138 mmol) and PhI(OAc)₂ (44.5 mg, 0.138 mmol) were added and the reaction was stirred 30 min before saturated sodium thiosulfate (4 mL) and EtOAc (5 mL) were added and the mixture was stirred at room temperature for 10 min before the layers were separated. The aqueous layer was extracted with EtOAc (4 x 5 mL) and the combined organics were dried (Na₂SO₄) and concentrated to a volume of approximately 1 mL, whereupon the product was precipitated from solution with pentane (6 mL). The suspension was filtered via Bucher funnel and collected to give 26.8 mg (82%) of **2.245** as a yellow solid: mp 167-170 °C; ¹H NMR for **2.245** (400 MHz, DMSO) δ 11.14 (s, 1 H), 7.39-7.28 (comp, 3 H), 7.27-7.15 (comp, 3 H), 7.09 (m, 2 H), 7.05-6.93 (comp, 3 H), 6.72 (d, J = 8.0 Hz, 1 H), 6.66-6.60 (comp, 3 H), 6.19 (s, 1 H), 4.96 (d, J = 15.8 Hz, 1 H), 4.71 (d, J = 15.8 Hz, 1 H), 3.13 (s, 3 H); ¹³C NMR for **2.245** (125 MHz, DMSO) δ 157.5, 157.2, 150.1, 149.0, 137.7, 136.8, 131.4, 129.4, 128.7, 128.3, 127.6, 127.1, 126.4, 124.6, 124.4, 123.4, 121.2, 118.8, 118.7, 118.2, 114.4, 111.6, 107.7, 87.2, 58.7, 49.8, 26.6; IR (neat) 3270, 1680, 1486, 1422 cm⁻¹; HRMS (ESI) *m/z* calcd for C₂₉H₂₃N₄O₃ (M+1), 475.17647; found 475.17572; mass spectrum, 475, 497 (base), 498.

NMR Assignments for 2.245:

^1H NMR for **2.245** (400 MHz, DMSO) δ 11.14 (s, 1 H, N-H), 7.39-7.28 (comp, 3 H, C25-H, C22-H, C12-H), 7.27-7.15 (comp, 3 H, C11-H, C8-H), 7.09 (m, 2 H, C10-H), 7.05-6.93 (comp, 3 H, C4-H, C23-H, C24-H), 6.72 (d, $J = 8.0$ Hz, 1 H, C20-H), 6.66-6.60 (comp, 3 H, C1-H, C5-H, C7-H), 6.19 (s, 1 H, C13-H), 4.96 (d, $J = 15.8$ Hz, 1 H, C8-H), 4.71 (d, $J = 15.8$ Hz, 1 H, C8-H), 3.13 (s, 3 H, C18-H); ^{13}C NMR for **2.245** (125 MHz, DMSO) δ 157.5 (C16), 157.2 (C15), 150.1 (C17), 149.0 (C19), 137.7 (C9), 136.8 (C21), 131.4 (C3), 129.4 (C14), 128.7 (C4), 128.3 (C11), 127.6 (C10), 127.1 (C26), 126.4 (C6), 124.6 (C12), 124.4 (C20), 123.4 (C5), 121.2 (C23), 118.8 (C24), 118.7 (C25), 118.2 (C13), 114.4 (C27), 111.6 (C22), 107.7 (C7), 87.2 (C1), 58.7 (C8), 49.8 (C2), 26.6 (C18).

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